

EP 0 296 612 B1



Europäisches Patentamt
Europ. an Pat. nt Offic
Office européen des brevets



⑪ Publication number:

0 296 612 B1

⑫ EUROPEAN PATENT SPECIFICATION

⑯ Date of publication of patent specification: 22.06.94 ⑯ Int. Cl. 5: C07D 471/14, A61K 31/47,
C07D 487/14, // (C07D471/14,
221:00,221:00,209:00)
⑯ Application number: 88110110.9
⑯ Date of filing: 24.06.88

The file contains technical information submitted
after the application was filed and not included in
this specification

⑯ Camptothecin derivatives and process for preparing same.

⑯ Priority: 25.06.87 JP 156495/87
⑯ Date of publication of application:
28.12.88 Bulletin 88/52
⑯ Publication of the grant of the patent:
22.06.94 Bulletin 94/25
⑯ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE
⑯ References cited:
EP-A- 0 088 642
GB-A- 2 056 973
CHEMICAL ABSTRACTS, vol. 90, no.13, 26th
March 1979, page 34, column 2, abstract no.
97494h, Columbus, Ohio, US ; J.A. ADAMOV-
ICS et al.: "Prodrug analogs of the antitumor
alkaloid camptothecin"
PATENT ABSTRACTS OF JAPAN, vol. 11, no.
47 (C-403)(2494), 13th February 1987 & JP-
A-61210032

⑯ Proprietor: KABUSHIKI KAISHA YAKULT HON-
SHA
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo 105(JP)
⑯ Inventor: Sawada, Seigo
Yakult Honsha
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo(JP)
Inventor: Nakata, Kenichiro
Yakult Honsha
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo(JP)
Inventor: Okajima, Satoru
Yakult Honsha
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo(JP)
Inventor: Nagai, Hisako
Yakult Honsha
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo(JP)
Inventor: Yaegashi, Takashi
Yakult Honsha
1-19, Higashishinbashi 1-chome
Minato-ku Tokyo(JP)

Not : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

J. Med. Chem. (1976) vol. 19, no. 5, pp.
675-679

Inventor: Tezuka, K. nichi
Yakult Honsha
1-19, Higashishinbashl 1-chom
Minato-ku Tokyo(JP)
Inventor: Miyasaka, Tadashi
1-27-11, Aobadai midori-ku
Yokohama-shi Kanagawa-ken(JP)

⑦ Representative: VOSSIUS & PARTNER
Postfach 86 07 67
D-81634 München (DE)

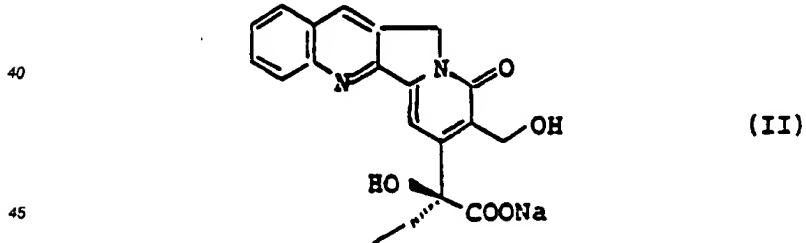
Description

The present invention relates to new camptothecin derivatives useful as anti-tumor agents or intermediates thereof and to a process for preparing such derivatives. More particularly, the present invention 5 relates to new prodrug-type camptothecin derivatives which exhibit excellent anti-tumor activity in the living body with a low level of toxicity as well as a process for the preparation of the new camptothecin derivatives starting from 7-ethylcamptothecin.

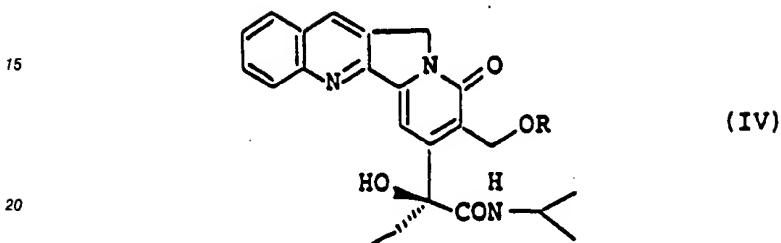
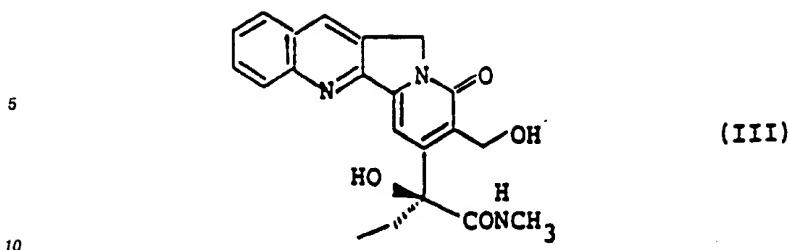
Camptothecin is an alkaloid extracted and isolated from *Camptotheca acuminata* (Nyssaceae), which 10 has a pentacyclic structure consisting of a characteristic fused 5-ring system consisting of quinoline (rings A and B), pyrrolidine (ring C), α -pyridone (ring D) and a six-membered lactone (ring E) and is distinguished by displaying a strong inhibitory activity towards biosynthesis of nucleic acid. In addition, camptothecin is a 15 unique anti-tumor substance characterized by its rapid and reversible action and its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 sarcoma in rats. 15 Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of high toxicity. Moreover, camptothecin and the majority of derivatives thereof are sparingly soluble in water and thus involve a problem in case of administration as medicaments.

Accordingly, a number of attempts have been made not only to reduce toxicity of camptothecin while 20 maintaining its anti-tumor activity by converting camptothecin chemically into its derivatives but also to make camptothecin and derivatives thereof easily soluble in water by chemical modifications of the camptothecin molecule or substituents therein. As one of such attempts, 10-hydroxy-substituted derivatives 25 among the camptothecin derivatives having been prepared hitherto are of interest in that the 10-hydroxy-substituted derivatives maintain an excellent anti-tumor activity with reduced toxicity. However, the derivatives were found to be sparingly soluble in water and therefore cannot be used as medicament without difficulty. As a method for making camptothecin derivatives soluble in water, for example, a ring-opening 30 reaction for the E-ring (lactone ring) of the camptothecin derivatives was used in the prior art to form an alkali metal salt of the carboxyl function. However, any chemical modification of the E-ring, including such ring-opening reaction, revealed only failure in maintaining anti-tumor activity and very poor improvement in toxicity [J. Med. Chem., 19, 675 (1976)].

According to a prior report, a water-soluble derivative of camptothecin of the formula (II) (hereinafter 35 referred to as camptothecin sodium salt) obtainable by the treatment of the E-ring (the lactone moiety) of camptothecin with an aqueous sodium hydroxide solution is not found to be useful as anti-tumor agent because of its toxicity of causing e.g. myelosuppression or hemorrhagic cystitis constituting a dose limiting factor [Cancer Chemother. Rep., 54, 461 (1970)].



50 M. C. Wani et al. reported that the anti-tumor activity of the camptothecin sodium salt is reduced to a fraction of what is found in a derivative with the lactone form [M. C. Wani et al., J. Med. Chem., 23, 554 (1980)]. It has been believed since then that the E-ring (the lactone moiety) of camptothecin, including the 55 20-hydroxyl group, is an essential partial structure for camptothecin to exhibit its anti-tumor activity. Any of the few previous reports on the chemical modification of the E-ring (the lactone moiety) revealed that the derivatives obtained by such chemical modification exhibit only little or no anti-tumor activity. For example, an E-ring (lactone)-opened derivative as the methylamide of the formula (III) shown below or as the isopropylamide of the formula (IV) shown below was reported to show very little or no activity [The Alkaloids, ed. by A. Brossi, Academic Press, N.Y., 1983 and J. Med. Chem., 22, 310 (1979)].



(wherein R is H, acetyl or propionyl.)

25 From the studies on various camptothecin derivatives prepared heretofore, it now becomes evident that chemical modifications in the E-ring, especially the E-ring opening, of camptothecin derivatives significantly adversely affect the anti-tumor activity. Under these circumstances, there is a great demand in this art for developing a new class of camptothecin derivatives maintaining strong anti-tumor activity even if chemically modified in the E-ring.

30 As a part of our studies on the preparation of water-soluble prodrug-type derivatives of camptothecin, we fixed our eyes on the E-ring of camptothecin derivatives to explore the possibility of converting them into a prodrug form. As the 17-hydroxy group of camptothecin in free form is spontaneously cyclized under neutral conditions with the partner carboxyl group to form a lactone ring, we have made extensive researches to solve simultaneously both problems of making the derivatives water-soluble and reconstructing the E-ring of the E-ring-opened derivatives in the living body after administration by masking the 17-hydroxy group of the E-ring-opened derivatives with such a protecting group as will be split off by hydrolysis by the action of an endogenous enzyme and converting the partner carboxyl group into a water-soluble carboxamide group.

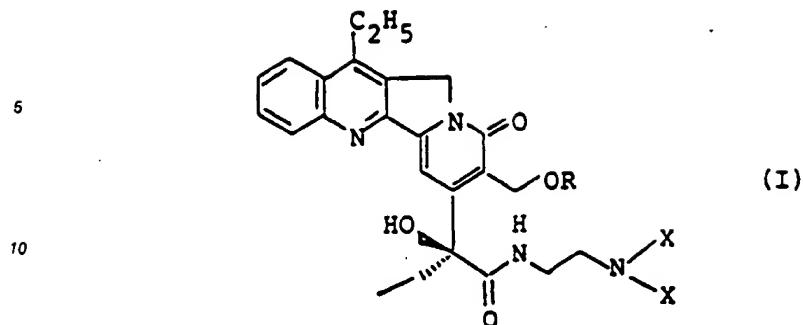
35 Accordingly, it is an object of the present invention to provide new prodrug-type camptothecin derivatives which exhibit excellent anti-tumor activity with a low level of toxicity.

40 It is another object of the present invention to provide new E-ring-opened camptothecin derivatives which are convertible into derivatives with the E-ring in the living body.

It is still another object of the present invention to provide a process for preparing water-soluble E-ring-opened camptothecin derivatives starting from 7-ethylcamptothecin.

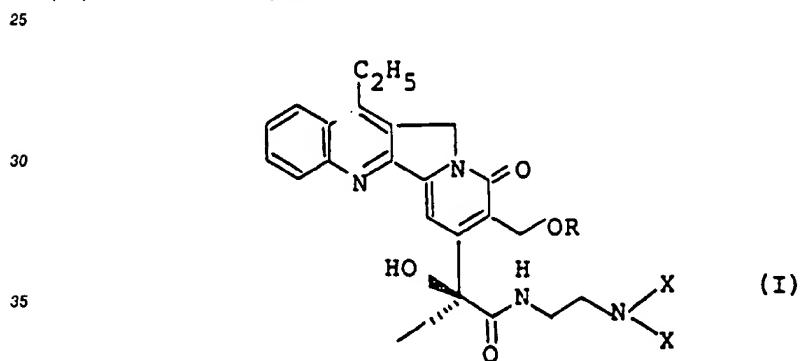
45 As a result of our extensive researches made for developing new water-soluble camptothecin derivatives to achieve the above mentioned objects, we have succeeded in opening the E-ring of 7-ethylcamptothecin with an N,N-dialkylethylenediamine to obtain E-ring-opened carboxamide derivatives which can easily be converted in the living body into the derivatives having the corresponding E-ring.

50 In accordance with one embodiment of the present invention there are provided new camptothecin derivatives of the general formula:



15 wherein X is a lower alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C₁-C₁₈ alkyl group; a lower alkyl group substituted by a halogen atom or a lower alkylthio, amino, acylamino, hydroxyl, lower alkoxy, phenoxy or naphthoxy or lower alkoxy carbonyl group; a C₃-C₁₉ alkenyl, C₃-C₁₉ alkynyl or C₃-C₈ cycloalkyl group; a C₃-C₈ cycloalkyl group substituted by an acylamino-lower alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, lower alkoxy carbonyl, lower alkyl, phenyl or lower alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thieryl group, and their acid addition salts formed at the amino group and quaternary ammonium salts.

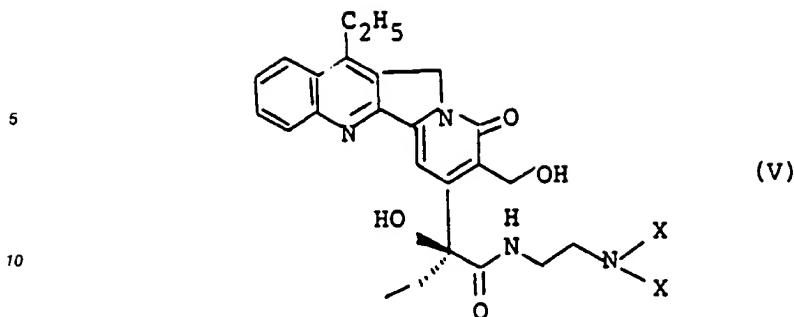
20 In accordance with another embodiment of the present invention, there is provided a process for the preparation of new camptothecin derivatives of the general formula:



40 wherein X is a lower alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C₁-C₁₈ alkyl group; a lower alkyl group substituted by a halogen atom or a lower alkylthio, amino, acylamino, hydroxyl, lower alkoxy, phenoxy or naphthoxy or lower alkoxy carbonyl group; a C₃-C₁₉ alkenyl, C₃-C₁₉ alkynyl or C₃-C₈ cycloalkyl group; a C₃-C₈ cycloalkyl group substituted by an acylamino-lower alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, lower alkoxy carbonyl, lower alkyl, phenyl or lower alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thieryl group, and their physiologically acceptable acid-addition salts at the amino group, which comprises treating 7-ethylcamptothecin with an ethylenediamine derivative of the general formula:

45 50 H₂N-CH₂CH₂-NX₂ (VI)

55 wherein X has the same meaning as given above,
to form a 7-ethyl-17-hydroxymethylcamptothecin-21-(2-dialkylamino)ethylamide of the general formula:



15 wherein X has the same meaning as given above,
and if necessary, acylating the resultant compound of the general formula (V) with a compound of the
general formula

Z-COY (VII)

20 wherein Y has the same meaning as given above and Z is a hydroxyl group, a halogen atom or the
grouping -O-COY, and if desired, converting the resultant compound of the general formula (I) into its
physiologically acceptable acid addition salt or quaternary ammonium salt or vice versa.

25 In the general formula (I) standing for the new compounds of this invention, the lower alkyl, alkoxy and
alkylthio groups have 1-6, preferably 1-4 carbon atoms in the alkyl moiety. Thus, the term "lower" is to be
interpreted as having 1-6 carbon atoms. These groups may be linear or branched in their alkyl moiety.
Illustrative of the lower alkyl groups and the linear or branched unsubstituted C₁-C₁₈ alkyl groups are, for
example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl,
decyl, undecyl, dodecyl, tetradecyl, hexadecyl and octadecyl. Examples of the lower alkoxy groups include
30 methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, pentoxy, hexoxy. Examples of the lower alkylthio include
alkylthio groups corresponding to the aforesaid alkoxy groups. Examples of the alkenyl groups with 3-19
carbon atoms include propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl,
dodecenyl, tetradecenyl, hexadecenyl, octadecenyl and nonadecenyl groups. Mentioned as the alkynyl
35 groups with 3-19 carbon atoms are alkynyl groups corresponding to the aforesaid alkenyl groups. The acyl
moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected
from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids,
and halogen- or hydroxy-substituted derivatives thereof.

40 In case the acyl group is derived from an amino acid, it may contain a protective group for the amino
group. A preferable acyl moiety is, for example, a lower alkanoyl or benzoyl group which may be
substituted.

Illustrative of the cycloalkyl groups are, for example, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl
and cyclooctyl groups, with cyclopropyl, cyclopentyl and cyclohexyl being preferable.

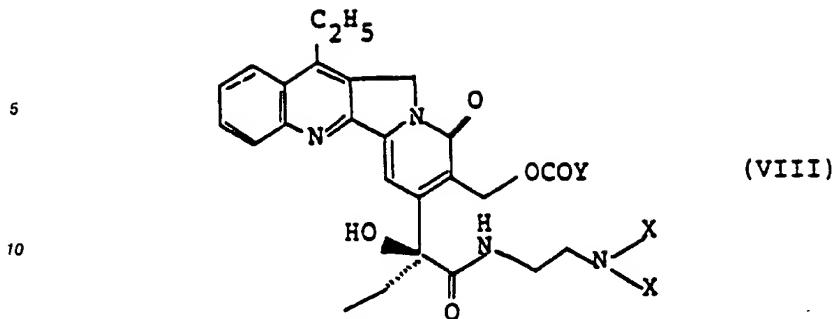
7-ethylcamptothecin used as the main starting material is commercially available or can be prepared
according to the process disclosed in U.S. Patent Re. 32,518.

45 Preferable examples of the N,N-di(lower alkyl)-ethylenediamine used for opening the E-ring of 7-
ethylcamptothecin include N,N-dimethyl-ethylenediamine, N,N-diethyl-ethylenediamine, N,N-dipropyl-
ethylenediamine and N,N-dibutyl-ethylenediamine.

50 The process of this invention for preparing the new camptothecin derivatives comprises the two steps of
treating 7-ethylcamptothecin with an N,N-di(lower alkyl)-ethylenediamine and optionally acylating the 17-
hydroxyl group of the resultant compound with a compound of the general formula:

Z-COY (VII)

55 wherein Y and Z have the same meanings as given above, to obtain a compound of the general formula:



15 wherein X, Y and Z have the same meanings as given above.

In the first step for the treatment with an N,N-di(lower alkyl)-ethylenediamine, 7-ethylcamptothecin is dissolved in an excess amount of the N,N-di(lower alkyl)-ethylenediamine. As the excess amount of the N,N-di(lower alkyl)-ethylenediamine functions as a reaction solvent, there is generally no necessity of using a reaction solvent additionally. The solution is then stirred preferably in a nitrogen atmosphere for a period 20 generally from 10 minutes to 5 hours, preferably from 30 minutes to 2 hours within the temperature range from room temperature to 100°C, preferably from 30 to 70°C. By raising the reaction temperature, the reaction time may be shortened accordingly. After completion of the reaction, the excess N,N-di(lower alkyl)-ethylenediamine is distilled off under reduced pressure. The residue is taken up in a solvent such as methylene chloride or chloroform and the solution is added to an inert solvent such as n-hexane in an 25 amount of several times as much as the solution whereby the resultant compound is precipitated as crystals which are then collected by filtration. 7-Ethyl-17-hydroxycamptothecin-21-[2-di(lower alkyl)]amino ethylamide as an E-ring-opened product is thus obtained in a theoretical yield. This compound can be shown by the general formula (V) and can optionally be acylated in the 17-hydroxy position thereof. This compound reverts to the starting compound, 7-ethylcamptothecin, when allowed to stand in a solution 30 thereof or subjected to column chromatography on silica gel.

In the subsequent step of the optional acylation, the reaction itself is carried out according to a usual manner for acylation of the hydroxyl group. The E-ring-opened camptothecin derivative of the general formula (V) is dissolved in a solvent and a catalytic amount of 4-N,N-dimethylaminopyridine is added to the solution. Illustrative of the solvent used for this acylation are, for example, methylene chloride, chloroform, 35 DMF, dimethylsulfoxide and ether. The solution is stirred under cooling, preferably under ice-cooling and a compound of the general formula (VII) as acylating agent alone or in a solvent as above mentioned is added, and the mixture is continuously stirred under cooling or at room temperature until the reaction is completed. Water is then added to the reaction mixture and then an aqueous solution of caustic alkali, for example, 1N-NaOH solution, is added to the mixture to make it weakly alkaline. The resultant compound is 40 extracted with methylene chloride or chloroform and the extract is washed with a saturated aqueous solution of edible salt. The organic phase is then dried over magnesium sulfate or sodium sulfate and then concentrated under reduced pressure until dryness. The residue is then subjected to column chromatography on silica gel whereby a 17-acylated compound of the general formula (VIII) is obtained in a moderate yield.

45 Alternatively, the 17-acylated compound can be obtained by treating a compound of the general formula (VII) with a condensing agent such as dicyclohexylcarbodiimide or the like mild dehydrating agent and then reacted with the E-ring-opened compound of the general formula (V) in the presence of N,N-dimethylaminopyridine, and can be purified in the same manner as described above.

The compounds of this invention represented by the general formula (I) can be converted, if desired, 50 into physiologically acceptable acid addition salts or quaternary salts thereof with proper inorganic or organic acids or alkyl or aryl halides, respectively. Examples of the inorganic and organic acids used for the preparation of acid addition salts include hydrohalic acids such as hydrochloric acid, sulfuric acid, methanesulfonic acid, alkanoic acids such as acetic acid, and alkanedicarboxylic acids such as tartaric acid, citric acid, etc. Preferable examples of the alkyl halide include methyl iodide and ethyl bromide. In order to 55 prepare these salts, the compound of the general formula (I) is incorporated with the acid or the alkyl halide in an equimolar amount and then the mixture is heated until dryness or lyophilized. The acid addition salts can be liberated by the treatment with an alkaline substance.

The acid addition salts are formed at the amino group of the thylenediamine moiety and the quaternary salts are formed at the tertiary amino group.

The new camptothecin derivatives of this invention are useful as medicaments or intermediates therefore. A recommended dose of the derivatives is generally 1-400 mg/kg of body weight in case of rat.

5 The present invention will now be illustrated in more detail by way of examples.

Example 1

(Preparation of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide)

10 7-Ethylcamptotecin(1.00g, 2.66mmol) was stirred in N,N-dimethylethylenediamine(20ml) for an hour at 50 °C under a N₂ atmosphere. After the stirring, the reaction mixture was evaporated to dryness under reduced pressure. The remaining solid was dissolved in dichloromethane, and the solution was poured into n-hexane(300ml). The precipitated crystals were filtrated by suction, whereupon the title compound was obtained(0.87g, 70.7% in yield) as yellow crystals.

15 m.p. 195~215 °C

Example 2

20 (Preparation of 7-ethyl-17-acetoxycamptothecin-21-(2-diethylamino)ethylamide)

(a) 7-Ethylcamptotecin(1.00g, 2.66mmol) was dissolved in N,N-diethyl-ethylenediamine(20ml), the reaction followed by the after-treatment was carried out in the same manner as described in Example 1, whereby 7-ethyl-17-hydroxycamptothecin-21-(2-diethylamino)ethylamide was obtained.

25 (b) Acetyl chloride(173μl, 2.44mmol) was added to the ice-cooled solution of 7-ethyl-17-hydroxycamptothecin-21-(2-diethylamino)ethyl amide, obtained by step(a), in dichloromethane(20ml), in the presence of 4-dimethylaminopyridine(100mg, 0.82mmol). After stirring for an hour under ice-cooling, water was added to the reaction mixture, and the aqueous phase was adjusted to weak basic conditions by adding 1N NaOH. After shaking, the organic phase was separated, washed with saturated aqueous solution of NaCl, dried over anhydrous MgSO₄, filtered, and then evaporated to dryness under reduced pressure. The residual material was purified through silica gel column chromatography with CHCl₃-MeOH as an eluent and crystallized from n-hexane to give the title compound as pale yellow crystals.

30 m.p. 177~181 °C

35 Example 3

(Preparation of 7-ethyl-17-benzoyloxycamptothecin-21-(2-diethylamino) ethylamide)

40 Using benzoyl chloride(311μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as yellow crystals. m.p. 151~164 °C IR_v (KBr)cm⁻¹;3350, 2930, 1700, 1650, 1590, 1510, 1450, 1270, 1100, 710.

Example 4

45 (Preparation of 7-ethyl-17-propionyloxycamptothecin-21-(2-diethylamino) ethylamide)

Using propionyl chloride(212μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as pale yellow crystals. m.p. 208~209.5 °C IR_v (KBr)cm⁻¹;3360, 2960, 1730, 1650, 1590, 1520, 1460, 1180, 760.

Example 5

55 (Preparation of 7-ethyl-17-butyryloxycamptothecin-21-(2-diethylamino) ethylamide)

Using butyryl chloride(253μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby

the title compound was obtained as pale yellow crystals.

m.p. 150-154 °C

IR ν (KBr)cm⁻¹; 3370, 2960, 1730, 1650, 1590, 1520, 1180, 760.

5 Example 6

(Preparation of 7-ethyl-17-butyryloxycamptothecin-21-(2-dimethylamino) ethylamide)

Using 21-(2-dimethylamino)ethylamide derivative and butyryl chloride(269 μ l, 2.59mmol) in place of 21-

10 (2-diethylamino)ethylamide derivative and acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as pale yellow crystals.

m.p. 164.5-166.5 °C

IR ν (KBr)cm⁻¹; 3370, 2960, 1730, 1650, 1590, 1520, 1460, 1180, 760.

15

Example 7

(Preparation of 7-ethyl-17-benzoyloxycamptothecin-21-(2-dimethylamino) ethylamide)

20 Using benzoyl chloride(331 μ l, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(142mg, 11.6% in yield).

m.p. 172-176 °C

IR ν (KBr)cm⁻¹; 3350, 2980, 1710, 1640, 1590, 1500, 1450, 1270, 1100, 715.

25 NMR(in CDCl₃) δ ppm; 1.09(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.35(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.18(6H, s, -N-(CH₃)₂), 2.34-2.41(3H, m, -CH₂CH₂N = and 20-CHH'CH₃), 2.44-2.51(1H, m, 20-CHH'CH₃), 3.08-3.14(2H, m, 7-CH₂CH₃), 3.19-3.25(1H, m, -NHCHH'CH₂N =), 3.32-3.39(1H, m, -NHCHH'CH₂N =), 5.15(2H, dd, J = 18.7Hz, 5-H₂), 5.76 and 5.87(two 1H's, d, J = 11.7Hz, 17-H₂), 7.35-7.39(3H, m, 17-O(C = O)Ph and -NHCH₂CH₂N =), 7.50(1H, t, J = 7.3Hz, 17-O(C = O)Ph), 7.55(1H, t, J = 7.3Hz, 10-H), 7.63(1H, s, 14-H), 7.73-30 (1H, t, J = 7.0Hz, 11-H), 7.93(1H, d, J = 8.4Hz, 9-H), 8.03(2H, d, J = 7.3Hz, 17-O(C = O)Ph), 8.13(1H, d, J = 8.4Hz, 12-H).

Example 8

35 (Preparation of 7-ethyl-17-(4-methoxybenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-methoxybenzoyl chloride(363 μ l, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(224mg, 17.4% in yield).

40 m.p. 176-177.5 °C

IR ν (KBr)cm⁻¹; 3400, 3300, 2960, 1690, 1660, 1640, 1600, 1500, 1450, 1260, 1240, 1160, 1090, 760.

45 NMR(in CDCl₃) δ ppm; 1.08(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.36(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.24(6H, s, -N-(CH₃)₂), 2.36-2.49(4H, m, -CH₂CH₂N = and 20-CH₂CH₃), 3.12(2H, q, 7-CH₂CH₃), 3.21-3.27 and 3.37-3.42- (two 1H's, m, -NHCH₂CH₂N =), 3.82(3H, s, -OCH₃), 5.17(2H, dd, 5-H₂), 5.70 and 5.85(two 1H's, d, J = 11.7Hz, 17-H₂), 6.85(2H, d, J = 8.8Hz, Arom), 7.57(1H, t, 10-H), 7.64(1H, s, 14-H), 7.74 (1H, t, 11-H), 7.96-8.00(3H, m, 9-H and Arom), 8.15(1H, d, 12-H).

Example 9

50 (Preparation of 7-ethyl-17-(4-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-fluorobenzoyl chloride(305 μ l, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(613mg, 48.5% in yield).

55 m.p. 167.2-169.5 °C

IR ν (KBr)cm⁻¹; 3400, 2970, 1710, 1650, 1600, 1500, 1455, 1270, 1110, 765.

NMR(in CDCl₃) δ ppm; 1.14(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.27(3H, t, J = 7.3Hz, 7-CH₂CH₃), 2.17(6H, s, -N-(CH₃)₂), 2.32-2.44(3H, m, CH₂CH₂N = and 20-CHH'CH₃), 2.57-2.64(1H, m, 20-CHH'CH₃), 2.89-3.01(2H, m,

7-CH₂CH₃), 3.07~3.15 and 3.33~3.41(two 1H's, m, -NHCH₂CH₂N=), 4.97(2H, dd, J=18.3Hz, 5-H₂), 5.80-(2H, d, J=11.7Hz, 17-H₂), 7.00(2H, t, J=8.8Hz, Arom), 7.35(1H, t, J=7.3Hz, 10-H), 7.59 (1H, s, 14-H), 7.61-(1H, d, 9-H), 7.70(1H, t, 11-H), 7.94(1H, d, J=8.1Hz, 12-H), 8.02(2H, dd, Arom).

5 Example 10

(Preparation of 7-ethyl-17-(4-bromobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-bromobenzoyl chloride(568mg, 2.59mmol) as an acid chloride, the reaction followed by the
10 after-treatment was carried out in the same manner as described in example 6, whereby the title compound
was obtained as pale yellow crystals(926mg, 66.4% in yield).

m.p. 176~179.5 °C

IR ν (KBr)cm⁻¹; 3350, 2980, 1710, 1670, 1650, 1595, 1510, 1450, 1270, 1095, 760.

NMR(in CDCl₃) δ ppm; 0.95(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.30(3H, t, J=7.3Hz, 7-CH₂CH₃), 2.39~2.48(2H,
15 m, 20-CH₂CH₃), 2.77(6H, s, -N(CH₃)₂), 2.99~3.22(4H, m, -CH₂CH₂N= and 7-CH₂CH₃), 3.36~3.44 and
3.88~3.93(two 1H's, m, -NHCH₂CH₂N=), 5.09(2H, dd, J=19.1Hz, 5-H₂), 5.76(2H, dd, J=11.7Hz, 17-H₂),
7.41 (2H, d, Arom), 7.54(1H, t, 10-H), 7.75~7.79(2H, m, 14-H and 11-H), 7.92(1H, d, 9-H), 8.05(1H, d, 12-H),
8.20(1H, br, -NHCH₂CH₂N=).

20 Example 11

(Preparation of 7-ethyl-17-(2-bromobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 2-bromobenzoyl chloride(568mg, 2.59mmol) as an acid chloride, the reaction followed by the
25 after-treatment was carried out in the same manner as described in example 6, whereby the title compound
was obtained as pale yellow crystals(324mg, 24.5% in yield).

m.p. 180~183.5 °C

IR ν (KBr)cm⁻¹; 3380, 3250, 2980, 1710, 1670, 1595, 1510, 1460, 1240, 1140, 1100, 940.

NMR(in CDCl₃) δ ppm; 1.14(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.31(3H, t, J=7.3Hz, 7-CH₂CH₃), 2.16(6H, s, -N-
30 (CH₃)₂), 2.29~2.41(3H, m, -CH₂CH₂N= and 20-CHH'CH₃), 2.54~2.63(1H, m, 20-CHH'CH₃), 2.94~3.19(3H,
m, 7-CH₂CH₃ and -NHCHH'CH₂N=), 3.32~3.38(1H, m, -NHCHH'CH₂N=), 5.05(2H, dd, J=19.1Hz, 5-H₂),
5.80(2H, s, 17-H₂), 7.41 (1H, t, 10-H), 7.46~7.49(2H, m, Arom), 7.54(1H, t, -NH-), 7.58 (1H, s, 14-H), 7.65(1H,
t, 11-H), 7.71(1H, d, 9-H), 7.84~7.87(2H, m, Arom), 8.00 (1H, d, J=7.3Hz, 12-H).

35 Example 12

(Preparation of 7-ethyl-17-propionyloxycamptothecin-21-(2-dimethylamino)ethylamide)

Using propionyl chloride(225 μ l, 2.59mmol) as an acid chloride, the reaction followed by the after-
40 treatment was carried out in the same manner as described in example 6, whereby the title compound was
obtained as pale yellow crystals(535mg, 47.7% in yield).

m.p. 137~154 °C

IR ν (KBr)cm⁻¹; 3360, 2970, 1760, 1730, 1650, 1595, 1510, 1460, 1170, 1130, 1070.

NMR(in CDCl₃) δ ppm; 1.12(6H, t, J=7.3Hz, 20-CH₂CH₃ and 17-O(C=O)CH₂CH₃), 1.30(3H, t, J=7.3Hz, 7-
45 CH₂CH₃), 2.26(6H, s, -N(CH₃)₂), 2.28~2.37(3H, m, CH₂CH₂N= and 20-CHH'CH₃), 2.42~2.56(3H, m, 20-
CHH'CH₃ and 17-O(C=O)CH₂CH₃), 2.91~3.06(2H, m, 7-CH₂CH₃), 3.25~3.33 and 3.43~3.51(two 1H's, m,
-NHCH₂CH₂N=), 4.99(2H, dd, J=18.3Hz, 5-H₂), 5.49(2H, d, J=11.7Hz, 17-H₂), 7.41(1H, t, 10-H), 7.53(1H,
s, 14-H), 7.65(1H, t, 11-H), 7.71(1H, d, 9-H), 7.99(1H, d, 12-H).

50 Example 13

(Preparation of 7-ethyl-17-(4-chlorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-chlorobenzoyl chloride(329 μ l, 2.59mmol) as an acid chloride, the reaction followed by the
55 after-treatment was carried out in the same manner as described in example 6, whereby the title compound
was obtained as pale yellow crystals(613mg, 47.2% in yield).

m.p. 167~188 °C

IR ν (KBr)cm⁻¹; 3360, 2970, 1710, 1670, 1650, 1590, 1510, 1450, 1280, 1090.

Example 14

(Preparation of 7-ethyl-17-(4-nitrobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its methanesulfonate)

5 To the ice-cooled solution of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in dichloromethane(20ml), 4-N,N-dimethylaminopyridine(100mg, 0.82mmol) and 4-nitrobenzoyl chloride(1.20g, 6.45mmol) were added. After stirring under ice-cooling for an hour, the reaction mixture was diluted with dichloromethane, washed with a saturated aqueous solution of NaHCO_3 and with a saturated aqueous solution of NaCl . The organic phase was separated, dried over anhydrous MgSO_4 , filtered, and then evaporated to dryness under reduced pressure. The residual material was purified through silica gel column chromatography with CHCl_3 - MeOH as an eluent and crystallized from CHCl_3 -n-hexane to give the title compound(633mg, 47.9% in yield) as pale yellow powder.
m.p. 153~158 °C (dec.)

15 IR ν (KBr)cm⁻¹; 3380, 2960, 2940, 1717, 1650, 1580, 1525, 1270.
NMR(CDCl_3) δ ppm; 1.13(3H, t, J = 7.3Hz, 20- CH_2CH_3), 1.35(3H, t, J = 7.7Hz, 7- CH_2CH_3), 2.16(6H, s, - $\text{N}(\text{CH}_3)_2$, 2.27~2.61(4H, m, - $\text{CH}_2\text{CH}_2\text{N} =$ and 20- CH_2CH_3), 3.00~3.39(4H, m, 7- CH_2CH_3 and $\text{NHCH}_2\text{CH}_2\text{N} =$), 5.13(2H, dd, J = 19.1Hz, 5- H_2), 5.36(1H, br, 20-OH), 5.85(2H, dd, J = 11.7Hz, 17- H_2), 7.37(1H, br-t, J = 5.1Hz, $\text{NHCH}_2\text{CH}_2\text{N} =$), 7.51(1H, t, 10-H), 7.59(1H, s, 14-H), 7.71(1H, t, 11-H), 7.86(1H, d, 9-H), 8.09(1H, d, 12-H), 8.15~8.25(4H, m, - C_6H_4 -p- NO_2).

20

Methanesulfonate

25 To the CHCl_3 solution of free compound(200mg, 0.33mmol) a 0.1M THF solution of methanesulfonic acid(5.0ml) was added. Then n-hexane (20ml) was added to the solution and the resulting precipitated crystals were filtrated and dried to give yellow crystals of methanesulfonate in quantitative yield.
IR ν (KBr)cm⁻¹; 3380, 2685, 1715, 1650, 1605, 1520, 1270, 1200.
NMR(DMSO-d_6) δ ppm; 0.92(3H, t, J = 7.3Hz, 20- CH_2CH_3), 1.33(3H, t, J = 7.7Hz, 7- CH_2CH_3), 2.18~2.29(2H, m, 20- CH_2CH_3), 2.31(3H, s, CH_3SO_3^-), 2.74 and 2.75(two 3H's, s, $\text{NH}^+(\text{CH}_3)_2$), 3.01~3.50(6H, m, 7- CH_2CH_3 and $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 5.36(2H, s, 5- H_2), 5.70(2H, dd, J = 11.0Hz, 17- H_2), 6.35~6.49(1H, br, 20-OH), 7.53(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 8.14 and 8.36(two 2H's, d, J = 8.8Hz, - C_6H_4 -p- NO_2), 8.20(1H, d, 9-H), 8.33(1H, d, 12-H), 8.47(1H, t, J = 5.9Hz, $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 9.14~9.34(1, br, $\text{NH}^+ =$).

Example 15

35 (Preparation of 7-ethyl-17-(4-trifluoromethylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide, its methanesulfonate, and hydrochloride)

40 Using 4-trifluoromethylbenzoyl chloride(1.35g, 6.45mmol) as an acid chloride in place of 4-nitrobenzoyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a pale yellow solid of the title compound(916 mg, 66.9% in yield) was obtained.
m.p. 144~148 °C (dec.)

45 IR ν (KBr)cm⁻¹; 3360, 2960, 2930, 1715, 1650, 1595, 1510, 1325, 1275, 1165, 1125, 1100.

45 Methanesulfonate

To the CHCl_3 solution of free compound(200mg) a 0.1M THF solution of methanesulfonic acid(4.7ml) was added. Then n-hexane(20ml) was added to the solution and the resulting precipitated crystals were collected by filtration and dried to give yellow crystals of methanesulfonate in quantitative yield.
50 IR ν (KBr)cm⁻¹; 3380, 2670, 1715, 1650, 1610, 1325, 1275, 1195, 1120, 1055.
NMR(DMSO-d_6) δ ppm; 0.91(3H, t, J = 7.3Hz, 20- CH_2CH_3), 1.33(3H, t, J = 7.7Hz, 7- CH_2CH_3), 2.24(2H, q, 20- CH_2CH_3), 2.34(3H, s, CH_3SO_3^-), 2.74 and 2.75(two 3H's, s, $\text{NH}^+(\text{CH}_3)_2$), 3.04~3.49(6H, m, 7- CH_2CH_3 and $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 5.35(2H, s, 5- H_2), 5.69(2H, dd, J = 11.0Hz, 17- H_2), 6.22~6.60(1H, br, 20-OH), 7.54(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91 and 8.11(two 2H's, d, - C_6H_4 -p- CF_3), 8.20(1H, d, 9-H), 8.31(1H, d, 12-H), 8.47(1H, t, J = 5.9Hz, $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 9.17~9.37(1H, br, $\text{NH}^+ =$).

Hydrochloride

To the suspension of free compound(200mg) in distilled water(5ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3360, 2670, 1715, 1650, 1595, 1510, 1325, 1275, 1120, 1100.

10 NMR(DMSO-d₆) δ ppm; 0.89(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J=7.7Hz, 7-CH₂CH₃), 2.26(2H, q, 20-CH₂CH₃), 2.72 and 2.73(two 3H's, s, NH⁺=(CH₃)₂), 3.00 ~3.56(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.34(2H, s, 5-H₂), 5.71(2H, dd, J=11.0Hz, 17-H₂), 6.35~6.70(1H, br, 20-OH), 7.57(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91 and 8.10(two 2H's, d, -C₆H₄-p-CF₃), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.48(1H, t, J=5.9Hz, -NHCH₂CH₂NH⁺ =), 9.90~10.10(1H, br, -NH⁺ =).

Example 16

15 (Preparation of 7-ethyl-17-(4-iodobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its methanesulfonate)

Using 4-iodobenzoyl chloride (1.00g, 3.75mmol) as an acid chloride in place of 4-nitrobenzoyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a pale yellow solid of the title compound(648mg, 43.2% in yield) was obtained.

20 m.p. 146~150 °C (dec.)

IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 1710, 1650, 1585, 1510, 1270, 1100.

Methanesulfonate

25 To the CHCl₃ solution of free compound(200mg) a 0.1M THF solution of methanesulfonic acid(4.2ml) was added. Then n-hexane(20ml) was added to the solution and the resulting precipitated crystals were filtrated and dried to give yellow crystals of methanesulfonate in quantitative yield.

IR ν (KBr)cm⁻¹; 3360, 2670, 1710, 1650, 1610, 1585, 1270, 1195, 1055.

30 NMR(DMSO-d₆) δ ppm; 0.90(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J=7.7Hz, 7-CH₂CH₃), 2.23(2H, m, 20-CH₂CH₃), 2.33(3H, s, CH₃SO₃⁻), 2.74 and 2.75(two 3H's, s, NH^{+(CH₃)₂), 3.02~3.48(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.35(2H, s, 5-H₂), 5.61(2H, dd, J=11.0Hz, 17-H₂), 6.24~6.55(1H, br, 20-OH, 7.52-(1H, s, 14-H), 7.66 and 7.91(two 2H's, d, C₆H₄-p-I), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 8.19(1H, d, 9-H), 8.30(1H, d, 12-H), 8.45(1H, t, J=5.5Hz, NHCH₂CH₂NH⁺ =), 9.19~9.35(1H, br, -NH⁺ =).}

35 Example 17
(Preparation of 7-ethyl-17-(1-naphthoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

40 Using 1-naphthoyl chloride(615mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(371mg, 27.9% in yield) were obtained.

m.p. 144~147 °C (dec.)

45 IR ν (KBr)cm⁻¹; 3380, 2960, 2925, 1705, 1650, 1595, 1510, 1275, 1240, 1195, 1135.

Hydrochloride

50 To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (193mg, 91.0% in yield).

IR ν (KBr)cm⁻¹; 3380, 1700, 1650, 1590, 1510, 1275, 1240, 1195, 1135.

55 NMR(DMSO-d₆) δ ppm; 0.90(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J=7.7Hz, 7-CH₂CH₃), 2.29(2H, q, 20-CH₂CH₃), 2.70 and 2.71(two 3H's, s, NH^{+=(CH₃)₂), 3.04 ~3.57(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.35(2H, s, 5-H₂), 5.74(2H, dd, J= 11.0Hz, 17-H₂), 6.40~6.60(1H, br, 20-OH), 7.51~7.71(4H, m, 14-H and Napht), 7.73(1H, t, 10-H), 7.86(1H, t, 11-H), 7.97~8.09(2H, m, Napht) 8.12~8.23(2H, m, 9-H and Napht), 8.29(1H, d, 12-H), 8.48(1H, t, J=5.5Hz, NHCH₂CH₂NH⁺ =), 8.83 (1H, d, J=8.4Hz, Napht), 9.98~10.12(1H, br, NH⁺ =).}

Example 18

(Preparation of 7-ethyl-17-(2-naphthoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

5

Using 2-naphthoyl chloride(615mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(538mg, 40.4% in yield) were obtained.

m.p. 179~183 °C (dec.)

10 IR ν (KBr)cm⁻¹; 3370, 2970, 2930, 1700, 1650, 1590, 1510, 1455, 1275, 1220, 1195.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

15 IR ν (KBr)cm⁻¹; 3380, 1705, 1650, 1595, 1280, 1225, 1195.

16 NMR(DMSO-d₆) δ ppm; 0.92(3H, t, J =7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J =7.7Hz, 7-CH₂CH₃), 2.18~2.40(2H, q, 20-CH₂CH₃), 2.70 and 2.71(two 3H's, s, NH⁺(CH₃)₂), 3.02~3.57(6H, m, 7-CH₂CH₃ and 20-NH₂CH₂NH⁺ =), 5.34(2H, s, 5-H₂), 5.74(2H, dd, J =11.0Hz, 17-H₂), 6.25~6.80(1H, br, 20-OH), 7.55~7.70(3H, m, 14-H and Napht), 7.74(1H, t, 10-H), 7.87(1H, t, 11-H), 7.92~8.13(4H, m, Napht), 8.21(1H, d, 9-H), 8.29(1H, d, 12-H), 8.50(1H, t, J =5.5Hz, -NH₂CH₂NH⁺ =), 8.56(1H, s, Napht), 10.16~10.34(1H, br, NH⁺ =).

Example 19

25

(Preparation of 7-ethyl-17-(2-furoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 2-furoyl chloride(422mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(662mg, 55.1% in yield) were obtained.

30 m.p. ~ 151 °C (dec.)

IR ν (KBr)cm⁻¹; 3380, 1710, 1650, 1595, 1295, 1175, 1115.

Hydrochloride

35

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.3ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

IR ν (KBr)cm⁻¹; 3300, 2950, 1710, 1650, 1600, 1510, 1470, 1295, 1175, 1110.

36 NMR(DMSO-d₆) δ ppm; 0.87(3H, t, J =7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J =7.7Hz, 7-CH₂CH₃), 2.10~2.35(2H, m, 20-CH₂CH₃), 2.72 and 2.73(two 3H's, s, NH⁺(CH₃)₂), 3.04~3.64(6H, m, 7-CH₂CH₃ and 20-NH₂CH₂NH⁺ =), 5.31(2H, s, 5-H₂), 5.64(2H, dd, J =11.0Hz, 17-H₂), 6.28~6.66(1H, br, 20-OH), 6.66(1H, dd, J =1.8 and 3.3Hz, Furano), 7.20(1H, d, Furano), 7.57(1H, s, 14-H), 7.73(1H, t, 10-H), 7.86(1H, t, 11-H), 7.94(1H, d, Furano), 8.19(1H, d, 9-H), 8.28(1H, d, 12-H), 8.45(1H, t, J =5.5 Hz, -NH₂CH₂NH⁺ =), 45 10.22~10.42(1H, br, NH⁺ =).

Example 20

(Preparation of 7-ethyl-17-(2-thenoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 2-thenoyl chloride(474mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(480mg, 38.8% in yield) were obtained.

55 m.p. 149~155 °C (dec.)

IR ν (KBr)cm⁻¹; 3370, 2970, 2960, 1695, 1645, 1595, 1515, 1260, 1090.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.2ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3370, 2670, 1695, 1645, 1590, 1520, 1260, 1090.
 NMR(DMSO-d₆) δ ppm; 0.88(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.13-2.38(2H, m, 20-CH₂CH₃), 2.72 and 2.74(two 3H's, s, NH⁺(CH₃)₂), 3.04-3.67(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.32(2H, s, 5-H₂), 5.66(2H, s, 17-H₂), 6.20-6.74(1H, br, 20-OH), 7.68-7.79(1H, m, 10-H and Thiopheno), 7.59(1H, s, 14-H), 7.67-7.80(2H, m, 10-H and Thiopheno), 7.86(1H, t, 11-H), 7.91(1H, d, J = 5.1Hz, Thiopheno), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.46(1H, t, J = 5.5Hz, NHCH₂CH₂NH⁺ =), 10.16-10.35(1H, br, NH⁺ =).

Example 21

15 (Preparation of 7-ethyl-17-cyclopropanecarbonyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

20 Using cyclopropanecarbonyl chloride(338mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(216mg, 18.8% in yield) were obtained.

m.p. 147-150 °C (dec.)

IR ν (KBr)cm⁻¹; 3375, 2965, 2930, 1715, 1645, 1595, 1515, 1455, 1395, 1175.

25 Hydrochloride

To the suspension of free compound(150mg) in distilled water(15ml) 0.1N HCl(3.4ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

30 IR ν (KBr)cm⁻¹; 3370, 2670, 1710, 1645, 1595, 1515, 1395, 1175.
 NMR(DMSO-d₆) δ ppm; 0.74-0.97(7H, m, 20-CH₂CH₃ and cyclo-Pr), 1.33(3H, t, J = 7.3Hz, 7-CH₂CH₃), 1.52-1.62(1H, m, cyclo-Pr), 2.10-2.31(2H, m, 20-CH₂CH₃), 2.76 and 2.77(two 3H's, s, NH⁺(CH₃)₂), 3.05-3.35(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.32(2H, s, 5-H₂), 5.37(2H, d, J = 11.0Hz, 17-H₂), 6.28-6.58 (1H, br, 20-OH), 7.54(1H, s, 14-H), 7.74(1H, t, 10-H), 7.86(1H, t, 11-H), 8.19(1H, d, 9-H), 8.30(1H, d, 12-H), 8.40(1H, t, J = 5.1Hz, -NHCH₂CH₂NH⁺ =), 10.08-10.28 (1H, br, NH⁺ =).

Example 22

40 (Preparation of 7-ethyl-17-(3-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 3-fluorobenzoyl chloride(512mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound (348mg, 27.6% in yield) were obtained.

45 m.p. 132-138 °C (dec.)

IR ν (KBr)cm⁻¹; 3370, 2970, 2930, 1715, 1650, 1590, 1510, 1445, 1275, 1200.

Hydrochloride

50 To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

IR ν (KBr)cm⁻¹; 3380, 2670, 1710, 1650, 1590, 1510, 1445, 1275, 1200.
 NMR(DMSO-d₆) δ ppm; 0.89(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J = 7.3Hz, 7-CH₂CH₃), 2.26(2H, q, 20-CH₂CH₃), 2.72 and 2.74(two 3H's, s, NH⁺(CH₃)₂), 3.05-3.31(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.34(2H, s, 5-H₂), 5.68(2H, dd, J = 11.0Hz, 17-H₂), 6.38-6.60(1H, br, 20-OH), 7.46-7.67(4H, m, 14-H and Arom), 7.70-7.80(2H, 10-H and Arom), 7.87(1H, t, 11-H), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.48(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.01-10.21(1H, -NHCH₂CH₂NH⁺ =).

Example 23

(Preparation of 7-ethyl-17-(2-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

5

Using 2-fluorobenzoyl chloride(512mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(445mg, 35.2% in yield) were obtained.

m.p. 154~160 °C (dec.)

10 IR ν (KBr)cm⁻¹; 3360, 2960, 2930, 1715, 1650, 1610, 1510, 1450, 1295, 1250.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

15 IR ν (KBr)cm⁻¹; 3360, 2670, 1710, 1650, 1610, 1515, 1450, 1295, 1250, 1220, 1120, 1080.

NMR(DMSO-d₆) δ ppm; 0.87(3H, t, J=7.0Hz, 20-CH₂CH₃), 1.32(3H, t, J=7.7Hz, 7-CH₂CH₃), 2.18~2.33(2H, m, 20-CH₂CH₃), 2.73 and 2.74(two 3H' s, s, NH⁺(CH₃)₂), 3.05~3.60(6H, m, 7-CH₂CH₃ and 20-NHCH₂CH₂NH⁺ =), 5.32(2H,s, 5-H₂), 5.67(2H, dd, J=11.0Hz, 17-H₂), 6.36~6.60(1H, br, 20-OH), 7.23~7.38(2H, m, Arom), 7.57(1H, s, 14-H), 7.60~7.69(1H, m, Arom), 7.74(1H, t, 10-H), 7.78~7.92(2H, m, 11-H and Arom), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.46(1H, t, J=5.5Hz, -NHCH₂CH₂NH⁺ =), 10.04~10.26(1H, -NHCH₂CH₂NH⁺ =).

25 Example 24

(Preparation of 7-ethyl-17-(trans-4-benzyloxycarbonylaminomethylcyclohexanecarbonyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

30 Using trans-4-benzyloxycarbonylaminomethylcyclohexanecarbonyl chloride(2.00g, 6.46mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(1.00g, 31.6% in yield) were obtained.

m.p. ~ 112 °C (dec.)

IR ν (KBr)cm⁻¹; 3310, 2925, 1715, 1650, 1595, 1510, 1450, 1250, 1170, 1140.

35

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(2.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

40 IR ν (KBr)cm⁻¹; 3280, 2920, 2590, 1710, 1650, 1600, 1510, 1450, 1235, 1170, 1140.

NMR(DMSO-d₆) δ ppm; 0.74~0.98(5H, m, 20-CH₂CH₃ and cyclo-Hex), 1.18~1.43 (6H, m, 7-CH₂CH₃ and cyclo-Hex), 1.61~1.78(2H, m, cyclo-Hex), 1.81~1.98 (2H, m, cyclo-Hex), 2.08~2.28(3H, m, 20-CH₂CH₃ and cyclo-Hex), 2.75 and 2.76(two 3H's, s, NH⁺(CH₃)₂), 2.83(2H, t-like, cyclo-Hex-CH₂NHCO₂CH₂Ph), 3.05~3.63(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 4.98(2H, s, CO₂CH₂Ph), 5.30 (2H, s, 5-H₂), 5.34(2H, dd, J=11.0Hz, 17-H₂), 6.37(1H, s, 20-OH), 7.23(1H, t, cyclo-Hex-CH₂NHCO₂CH₂Ph), 7.25~7.40(5H, m, Ph), 7.55(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.37(1H, t, J=5.5 Hz, -NHCH₂CH₂NH⁺ =), 9.98~10.14(1H, br, -NHCH₂CH₂NH⁺ =).

50 Example 25

(Preparation of 7-ethyl-17-crotonyloxycamptothecin-21-(2-dimethylamino) ethylamide and its hydrochloride)

Using crotonyl chloride(337mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(230mg, 20.1% in yield) were obtained.

m.p. 147~148 °C (dec.)

IR ν (KBr)cm⁻¹; 3355, 2970, 2960, 1710, 1650, 1595, 1510, 1180.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.6ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3380, 2670, 1705, 1650, 1595, 1515, 1180.
 NMR(DMSO-d₆) δ ppm; 0.86(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 1.85(3H, d, J = 7.0Hz, CH = CHCH₃), 2.21(2H, q, 20-CH₂CH₃), 2.75 and 2.76(two 3H's, s, NH⁺(CH₂)₂), 3.03~3.60(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.30(2H, s, 5-H₂), 5.42(2H, dd, J = 11.0Hz, 17-H₂), 5.85(1H, d, J = 15.4Hz, 10-CH = CH-CH₃), 6.25~6.58(1H, br, 20-OH), 6.87(1H, dq, CH = CHCH₃), 7.54(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.18(1H, d, 9-H), 8.28(1H, d, 12-H), 8.39(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.13~10.31(1H, br, -NHCH₂CH₂NH⁺ =).

Example 26

15 (Preparation of 7-ethyl-17-caproyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using caproyl chloride(435mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of

20 the title compound(226mg, 18.7% in yield) were obtained.

m.p. 134~137 °C (dec.)

IR ν (KBr)cm⁻¹; 3360, 2925, 1725, 1645, 1590, 1510, 1455, 1170.

Hydrochloride

25 To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.4ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

IR ν (KBr)cm⁻¹; 3370, 2950, 2670, 1720, 1650, 1595, 1510, 1455, 1170.

30 NMR(DMSO-d₆) δ ppm; 0.72~0.98(6H, m, 20-CH₂CH₃ and CH₂(CH₂)₃CH₃), 1.17~1.61(9H, m, 7-CH₂CH₃ and CH₂(CH₂)₃CH₃), 2.10~2.33(4H, m, 20-CH₂CH₃ and CH₂(CH₂)₃CH₃), 2.75 and 2.76(two 3H's, s, NH⁺(CH₂)₂), 3.05~3.65(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.29(2H, s, 5-H₂), 5.38(2H, dd, J = 11.0Hz, 17-H₂), 6.30~6.50(1H, br, 20-OH), 7.56(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.38(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.15~10.32(1H, br, -NHCH₂CH₂NH⁺ =).

35

Example 27

(Preparation of 7-ethyl-17-cinnamoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride).

40

Using cinnamoyl chloride(538mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of

the title compound(447mg, 34.9% in yield) were obtained.

m.p. 140~143 °C (dec.)

45 IR ν (KBr)cm⁻¹; 3360, 2960, 2930, 1705, 1645, 1595, 1510, 1165.

Hydrochloride

50 To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (204mg, 96.2% in yield).

IR ν (KBr)cm⁻¹; 3340, 2670, 1700, 1650, 1595, 1510, 1165.

NMR(DMSO-d₆) δ ppm; 0.89(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.24(2H, q, 20-CH₂CH₃), 2.73 and 2.74(two 3H's, s, NH⁺ = (CH₂)₂), 3.03~3.60(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =),

55 5.32(2H, s, 5-H₂), 5.54(2H, dd, J = 11.0Hz, 17-H₂), 6.32~6.58(1H, br, 20-OH), 6.62(1H, d, J = 16.1Hz, CH = CHPh), 7.34~7.48(3H, m, Ph), 7.56(1H, s, 14-H), 7.64(1H, d, J = 16.1Hz, CH = CHPh), 7.64~7.80(3H, m, 10-H and Ph), 7.87(1H, t, 11-H), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H) 8.44(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.15~10.38(1H, br, -NHCH₂CH₂NH⁺ =).

Example 28

(Preparation of 7-ethyl-17-phenylacetoxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

5

Using phenylacetyl chloride(499mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(233mg, 18.6% in yield) were obtained.

m.p. 108~114 °C (dec.)

10 IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 1725, 1645, 1590, 1510, 1450, 1140.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

15 IR ν (KBr)cm⁻¹; 3300, 2670, 1720, 1650, 1595, 1510, 1140.

NMR(DMSO-d₆) δ ppm; 0.81(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.17(2H, q, 20-CH₂CH₃), 2.74 and 2.75(two 3H's, s, NH⁺ = (CH₃)₂), 3.02~3.63(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =),

20 3.64(2H, s, CH₂Ph), 5.30(2H, s, 5-H₂), 5.44(2H, dd, J = 11.0Hz, 17-H₂), 6.32~6.50(1H, br, 20-OH), 7.20~7.41(5H, m, Ph), 7.56(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.38(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.15~10.33(1H, br, -NHCH₂CH₂NH⁺ =).

Example 29

25

(Preparation of 7-ethyl-17-(4-phenylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-phenylbenzoyl chloride(700mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(214mg, 15.4% in yield) were obtained.

m.p. 197~201 °C (dec.)

IR ν (KBr)cm⁻¹; 3380, 3310, 2960, 2930, 1700, 1655, 1595, 1510, 1270, 1100.

35 Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(2.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

40 IR ν (KBr)cm⁻¹; 3360, 2675, 1700, 1645, 1595, 1510, 1270, 1100.

NMR(DMSO-d₆) δ ppm; 0.91(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.17~2.34(2H, m, 20-CH₂CH₃), 2.72 and 2.73(two 3H's, s, NH⁺ = (CH₃)₂), 3.03~3.58(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =),

45 5.35(2H, s, 5-H₂), 5.67(2H, dd, J = 11.6Hz, 17-H₂), 6.41~6.53(1H, br, 20-OH), 7.36~7.56(3H, m, Arom), 7.58(1H, s, 14-H), 7.65~7.80(3H, m, 10-H and Arom), 7.81(2H, d, J = 8, 1Hz, Arom), 7.87(1H, t, 11-H), 7.99(2H, d, Arom), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.47(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 9.92~10.09(1H, br, -NHCH₂CH₂NH⁺ =).

Example 30

50 (Preparation of 7-ethyl-17-cyclohexanecarbonyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using cyclohexanecarbonyl chloride(474mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(378mg, 30.6% in yield) were obtained.

m.p. 119~123 °C (dec.)

IR ν (KBr)cm⁻¹; 3360, 2930, 2850, 1720, 1650, 1595, 1510, 1450, 1245, 1165.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3350, 2930, 2675, 1715, 1645, 1595, 1510, 1450, 1170.

NMR(DMSO-d₆) δ ppm; 0.85(3H, t, J=7.3Hz, 20-CH₂CH₃), 1.10~1.46(8H, m, 7-CH₂CH₃ and cyclo-Hex), 1.50~1.90(5H, m, cyclo-Hex), 2.10~2.35(3H, m, 20-CH₂CH₃ and cyclo-Hex), 2.75(6H, s, NH⁺(CH₃)₂), 3.05~3.65(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.29(2H, s, 5-H₂), 5.36(2H, dd, J=11.0Hz, 17-H₂), 10 6.41(1H, s, 20-OH), 7.56(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.38(1H, t, J=5.5Hz, -NHCH₂CH₂NH⁺ =), 10.20~10.43(1H, br, -NHCH₂CH₂NH⁺ =).

Example 31

15 (Preparation of 7-ethyl-17-stearoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using stearoyl chloride(978mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(221mg, 14.0% in yield) was obtained.

20 IR ν (CHCl₃)cm⁻¹; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(3.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

25 IR ν (KBr)cm⁻¹; 3340, 2915, 2845, 2680, 1720, 1645, 1590, 1510, 1460, 1165.

NMR(DMSO-d₆) δ ppm; 0.85(6H, t, 20-CH₂CH₃ and CH₂(CH₂)₅CH₃), 1.08~1.59 (33H, m, 7-CH₂CH₃ and CH₂(CH₂)₅CH₃), 2.12~2.30(4H, m, 20-CH₂CH₃ and CH₂(CH₂)₅CH₃), 2.76(6H, s, NH⁺(CH₃)₂), 3.03~3.63-30 (6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.28(2H, s, 5-H₂), 5.37(2H, dd, J=11.0Hz, 17-H₂), 6.37(1H, s, 20-OH), 7.55(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.37(1H, t, J=5.7Hz, -NHCH₂CH₂NH⁺ =), 10.07~10.22(1H, br, -NHCH₂CH₂NH⁺ =).

Example 32

35 (Preparation of 7-ethyl-17-oleoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using oleoyl chloride(972mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of solid title compound(202mg, 12.9% in yield) was obtained.

40 IR ν (CHCl₃)cm⁻¹; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

45 To the suspension of free compound(163mg) in distilled water(20ml) 0.1N HCl(2.5ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a pale yellow amorphous solid in quantitative yield.

IR ν (KBr)cm⁻¹; 3340, 2920, 2835, 2685, 1720, 1645, 1595, 1510, 1455.

NMR(DMSO-d₆) δ ppm; 0.74~0.97(6H, m, 20-CH₂CH₃ and (CH₂)₇CH=CH(CH₂)₇CH₃), 1.11~2.05(29H,m, 7-CH₂CH₃ and -CH₂(CH₂)₆CH=CH(CH₂)₇CH₃), 2.11~2.30(4H, m, 20-CH₂CH₃ and -COCH₂-), 2.75(6H, s, NH⁺(CH₃)₂), 3.03~3.62(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.20~5.50(6H, m, 5-H₂, 17-H₂ and -CH=CH-), 6.38 (1H, s, 20-OH), 7.55(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.36(1H, t, J=5.5Hz, -NHCH₂CH₂NH⁺ =), 10.03~10.21(1H, br, -NHCH₂CH₂NH⁺ =).

Example 33

(Preparation of 7-ethyl-17-(4-methoxycarbonylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

5 Using 4-methoxycarbonylbenzoyl chloride(542mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow solid of the title compound(279mg, 24.5% in yield) was obtained.
m.p. 192~194 °C (dec.)
10 IR ν (KBr)cm⁻¹; 3360, 2960, 2930, 1720, 1650, 1590, 1515, 1270, 1110, 1100.

Hydrochloride

15 To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (208mg, 98.1% in yield).
IR ν (KBr)cm⁻¹; 3360, 2675, 1710, 1650, 1595, 1510, 1270, 1115, 1100.
NMR(DMSO-d₆) δ ppm; 0.89(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.17~2.34(2H, m, 20-CH₂CH₃), 2.72 and 2.73(two 3H's, s, NH⁺ = (CH₃)₂), 3.03~3.61(6H, m, 7-CH₂CH₃ and 20 NHCH₂CH₂NH⁺ =), 3.88(3H, s, CO₂CH₃), 5.33(2H, s, 5-H₂), 5.70(2H, dd, J = 11.0Hz, 17-H₂), 6.32~6.64(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.74(1H, t, 10-H), 7.86(1H, t, 11-H), 8.03 and 8.07(two 2H's, s, C₆H₄ CO₂CH₃), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.48(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.09~10.25(1H, br, -NHCH₂CH₂NH⁺ =).

25 Example 34

(Preparation of 7-ethyl-17-ethylsuccinylloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

30 Using ethylsuccinyl chloride(449mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow solid of the title compound(253mg, 23.5% in yield) was obtained.
m.p. 120~121 °C (dec.)
IR ν (KBr)cm⁻¹; 3370, 2970, 2930, 1730, 1645, 1590, 1155.

35 Hydrochloride

40 To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (200mg, 94.3% in yield).
IR ν (KBr)cm⁻¹; 3370, 2670, 2930, 2680, 1725, 1645, 1595, 1515, 1155.
NMR(DMSO-d₆) δ ppm; 0.86(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.19(3H, t, J = 7.3Hz, -CO₂CH₂CH₃), 1.33(3H, t, J = 7.3Hz, 7-CH₂CH₃), 2.21(2H, q, 20-CH₂CH₃), 2.54(4H, br, CH₂CH₂CO₂Et), 2.75 and 2.77(two 3H's, s, NH⁺(CH₃)₂), 3.05~3.72(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 4.07(2H, q, CO₂CH₂CH₃), 5.29(2H, s, 5-H₂), 5.42 (2H, dd, J = 10.6Hz, 17-H₂), 6.22~6.62(1H, br, 20-OH), 7.55(1H, s, 14-H), 7.72 (1H, t, 10-H), 7.85(1H, t, 11-H), 8.18(1H, d, 9-H), 8.27(1H, d, 12-H), 8.38(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.26~10.47(1H, br, -NHCH₂CH₂NH⁺ =).

Example 35

50 (Preparation of 7-ethyl-17-linoleoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

55 Using linoleoyl chloride(816mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(280mg, 21.2% in yield) was obtained.
IR ν (CHCl₃)cm⁻¹; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

To the suspension of free compound(250mg) in distilled water(25ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3280, 2920, 2850, 2680, 1720, 1650, 1600, 1510, 1455, 1170.
 NMR(DMSO-d₆) δ ppm; 0.73~0.95(6H, m, 20-CH₂CH₃ and -(CH₂)₇CH=CHCH₂CH=CH-(CH₂)₄CH₃),
 1.06~1.62(23H, m, 7-CH₂CH₃ and -CH₂(CH₂)₆CH=CHCH₂CH=CH-(CH₂)₄CH₃), 1.92~2.06(2H, m,
 =CHCH₂CH=), 2.11~2.30(4H, m, 20-CH₂CH₃ and -COCH₂-), 2.75(6H, s, NH^{+(CH₃)₂}), 3.00~3.63(6H, m, 7-
 10 CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.18~5.50(8H, m, 5-H₂, 17-H₂ and -CH=CH-x2), 6.38(1H, s, 20-OH), 7.55
 (1H, s, 14-H₁), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.35(1H, t, J = 5.8Hz,
 -NHCH₂CH₂NH⁺ =), 9.95~10.50(1H, br, -NHCH₂CH₂NH⁺ =).

Example 36

15 (Preparation of 7-ethyl-17-(4-chlorobutyryloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-chlorobutyryl chloride(385mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(227mg, 22.0% in yield) were obtained.

m.p. ~199 °C (dec.)

IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 1725, 1645, 1590, 1510, 1455, 1210, 1185, 1140.
 NMR(CDCl₃) δ ppm; 1.09(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.35(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.03~2.15(2H, m,
 25 CH₂CH₂CH₂Cl), 2.22(6H, s, -N(CH₃)₂), 2.25~2.57(6H, m, -CH₂CH₂N =, CH₂CH₂CH₂Cl and 20-CH₂CH₃),
 3.01~3.48(4H, m, 7-CH₂CH₃ and NHCH₂CH₂N =), 3.61(2H, t, J = 6.6Hz, CH₂CH₂CH₂Cl), 5.11(2H, dd,
 J = 18.7Hz, 5-H₂), 5.13(1H, s, 20-OH), 5.53(2H, dd, J = 11.7Hz, 17-H₂), 7.35(1H, t, -NHCH₂CH₂N =),
 7.52~7.58(2H, m, 10-H and 14-H), 7.73(1H, m, 11-H), 7.93(1H, d, 9-H), 8.12(1H, d, 12-H).

30 Hydrochloride

To the suspension of free compound(150mg) in distilled water(10ml) 0.1N HCl(3.2ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

35 IR ν (KBr)cm⁻¹; 3280, 2970, 2930, 2675, 1720, 1645, 1595, 1510, 1450.
 NMR(DMSO-d₆) δ ppm; 0.86(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, 7-CH₂CH₃), 1.93~2.05(2H, m,
 CH₂CH₂CH₂Cl), 2.21(2H, q, 20-CH₂CH₃), 2.43(2H, t, J = 7.3Hz, CH₂CH₂CH₂Cl), 2.75 and 2.76(two 3H's, s,
 NH^{+(CH₃)₂}), 3.04~3.62(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 3.68(2H, t, J = 6.6Hz, CH₂CH₂CH₂Cl),
 5.30(2H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.39(1H, t,
 40 J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.11~10.27(1H, br, -NHCH₂CH₂NH⁺ =).

Example 37

45 (Preparation of 7-ethyl-17-(S)-(-)-N-(trifluoracetyl)prolyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using (S)-(-)-N-(trifluoracetyl)prolyl chloride (0.1M solution in dichloromethane, 18.2ml) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(200mg, 16.8% in yield) were obtained.

50 m.p. ~152 °C (dec.)
 IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 1740, 1690, 1650, 1595, 1510, 1450, 1235, 1200, 1140.
 NMR(CDCl₃) δ ppm; 1.06(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.38(3H, t, J = 7.7Hz, 7-CH₂CH₃), 1.94~2.53(14H, m,
 -N(CH₃)₂, -CH₂CH₂N =, Proline, and 20-CH₂CH₃), 3.17 (2H, q, 7-CH₂CH₃), 3.25~3.50(2H, m,
 NHCH₂CH₂N =), 3.65~3.95(2H, m, Proline), 4.37(1H, br, 20-OH), 4.42~4.53(1H, m, Proline), 5.19(2H, dd,
 55 J = 18, 7Hz, 5-H₂), 5.68(1H, dd, J = 11.0Hz, 17-H₂), 7.46(1H, t, J = 5.0Hz, -NHCH₂CH₂N =), 7.64(1H, t, 10-H),
 7.74(1H, s, 14-H), 7.78(1H, t, 11-H), 8.08(1H, d, 9-H), 8.21(1H, d, 12-H).

Hydrochlorid

To the suspension of free compound(150mg) in distilled water(10ml) 0.1N HCl(2.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.

5 IR ν (KBr)cm⁻¹; 3370, 2965, 2675, 1735, 1685, 1650, 1595, 1510, 1455, 1230, 1205, 1145.

10 NMR(DMSO-d₆) δ ppm; 0.84(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, J = 7.7Hz, 7-CH₂CH₃), 1.80-2.38(6H, m, Proline and 20-CH₂CH₃), 2.75 and 2.76(two 3H's, s, NH⁺(CH₃)₂), 3.01-3.82(8H, m, 7-CH₂CH₃, NHCH₂CH₂N =, and Proline), 4.43-4.62(1H, m, Proline), 5.29(2H, s, 5-H₂), 5.45(2H, dd, J = 11.0Hz, 17-H₂), 6.30-6.70(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.18(1H, d, 9-H), 8.28(1H, d, 12-H), 8.40(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.20-10.44(1H, br, -NHCH₂CH₂NH⁺ =).

Example 38

15 (Preparation of 7-ethyl-17-(4-ethylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-ethylbenzoyl chloride(460mg, 2.73mmol) as an acid chloride the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(763mg, 70.4% in yield) were obtained.

20 m.p. 140-144 °C (dec.)

IR ν (KBr)cm⁻¹; 3380, 2960, 2930, 1710, 1650, 1605, 1510, 1455, 1270, 1105.

Hydrochloride

25 To the suspension of free compound(300mg) in distilled water(20ml) 0.1N HCl(5.5ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (295mg, 92.6% in yield).

IR ν (KBr)cm⁻¹; 3360, 2670, 1700, 1645, 1595, 1510, 1275, 1105.

30 NMR(DMSO-d₆) δ ppm; 0.88(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.18(3H, t, J = 7.7Hz, C₆H₄-CH₂CH₃), 1.32(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.16-2.35(2H, m, 20-CH₂CH₃), 2.66(2H, q, C₆H₄CH₂CH₃), 2.70 and 2.72(two 3H's, s, NH⁺(CH₃)₂), 3.00-3.59(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.33(2H, s, 5-H₂), 5.62(2H, dd, J = 11.0Hz, 17-H₂), 6.36-6.57(1H, br, 20-OH), 7.33(2H, d, J = 8.1Hz, Arom), 7.58(1H, s, 14-H), 7.73(1H, t, 10-H), 7.82(2H, d, Arom), 7.88(1H, t, 11-H), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.44(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.02-10.22(1H, br, -NHCH₂CH₂NH⁺ =).

Example 39

40 (Preparation of 7-ethyl-17-(3-methylthiopropionyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 3-methylthiopropionyl chloride(378mg, 2.75mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(766mg, 74.4% in yield) were obtained.

45 m.p. 96-103 °C (dec.)

IR ν (KBr)cm⁻¹; 3350, 2960, 2930, 1730, 1645, 1590, 1510, 1455, 1250, 1215, 1185, 1140.

Hydrochloride

50 To the suspension of free compound (300mg) in distilled water(20ml) 0.1N HCl(5.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (314mg, 98.4%, in yield).

IR ν (KBr)cm⁻¹; 3355, 2675, 1725, 1645, 1595, 1515.

55 NMR(DMSO-d₆) δ ppm; 0.86(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.33(3H, t, 7-CH₂CH₃), 2.07(3H, s, SCH₃), 2.22-2.57 and 2.69(two 3H's, t, COCH₂CH₂SCH₃), 2.75 and 2.76(two 3H's, s, NH⁺(CH₃)₂), 3.03-3.68(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.29(2H, s, 5-H₂), 5.42(2H, dd, J = 11.0Hz, 17-H₂), 6.25-6.58(1H, br, 20-OH), 7.55(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.39(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.18-10.44(1H, br, -NHCH₂CH₂NH⁺ =).

Example 40

(Preparation of 7-ethyl-17-(pivaloyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

5 Using pivaloyl chloride(329mg, 2.75mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(362mg, 36.3% in yield) were obtained.
 m.p. 202~204 °C (dec.)
 IR ν (KBr)cm⁻¹; 3400, 3250, 2960, 1715, 1670, 1645, 1585, 1515, 1455, 1280, 1160.

10

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(4.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (200mg, 93.9% in yield).

15 IR ν (KBr)cm⁻¹; 3360, 2960, 2685, 1710, 1645, 1595, 1510, 1280, 1155.
 NMR(DMSO-d₆) δ ppm; 0.85(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.14(9H, s, C(CH₃)₃), 1.33 (3H, t, 7-CH₂CH₃),
 2.10(2H, m, 20-CH₂CH₃), 2.75 and 2.76(two 3H's, s, NH⁺(CH₃)₂), 3.05~3.67(6H, m, 7-CH₂CH₃ and
 NHCH₂CH₂NH⁺ =), 5.29(2H, dd, J = 18.7Hz, 5-H₂), 5.35(2H, dd, J = 11.0Hz, 17-H₂), 6.27~6.56(1H, br, 20-
 OH), 7.60 (1H, s, 14-H), 7.72(1H, t, 10-H), 7.84(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.39(1H, t,
 J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 10.18~10.40(1H, br, -NHCH₂CH₂NH⁺ =).

20

Example 41

25 (Preparation of 7-ethyl-17-phenoxyacetoxycamptothecin-21-(2-dimethylamino)ethylamide)

Using phenoxyacetyl chloride(551mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(161mg) was obtained, which was crystallized from CHCl₃-n-hexane to give yellow crystals-(62mg, 4.8% in yield).

30 m.p. 112~117 °C (dec.)

IR ν (KBr)cm⁻¹; 3360, 2960, 2920, 1750, 1650, 1595.
 NMR(CDCl₃) δ ppm; 1.07(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.35(3H, t, J = 7.7Hz, 7-CH₂CH₃), 2.19(6H, s, N-(CH₃)₂), 2.22~2.57(4H, m, -CH₂CH₂N = and 20-CH₂CH₃), 3.10(2H, q, 7-CH₂CH₃), 3.24~3.46(2H, m,
 NHCH₂CH₂N =), 4.64(2H, s, COCH₂OPh), 4.93~5.28(1H, br, 20-OH), 5.09(2H, dd, J = 18.7Hz, 5-H₂), 5.65-
 (1H, dd, J = 11.4Hz, 17-H₂), 6.82~7.03(3H, m, OPh), 7.21~7.31(2H, m, OPh), 7.36(1H, t, J = 5.5Hz,
 NHCH₂CH₂N =), 7.52(1H, t, 10-H), 7.55(1H, s, 14-H), 7.72(1H, t, 11-H), 7.88(1H, d, 9-H), 8.09(1H, d, 12-H).

35

Example 42

40

(Preparation of 7-ethyl-17-(3-ethoxypropionyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

To the ice-cooled solution of 3-ethoxypropionic acid (323mg, 2.73 mmol) in dichloromethane, N,N'-dicyclohexylcarbodiimide(DCC, 846mg, 4.10mmol) was added and the reaction mixture was stirred for 0.5 hour. After adding the solution of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in dichloromethane(10ml) and 4-N,N-dimethylaminopyridine(100mg, 0.82mmol), the reaction mixture was stirred for an hour under ice-cooling and then for an hour at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were purified through silica gel column chromatography with CHCl₃-MeOH as an eluent and crystallized from CHCl₃-n-hexane to give yellow crystals of the title compound (50mg, 4.9% in yield).

45 m.p. 119~123 °C (dec.)

IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 2860, 1730, 1645, 1590, 1515, 1455, 1180.
 NMR(CDCl₃) δ ppm; 1.07(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.17(3H, t, J = 7.0Hz, OCH₂CH₃), 1.36(3H, t,
 J = 7.7Hz, 7-CH₂CH₃), 2.23(6H, s, -N(CH₃)₂), 2.24~2.53(4H, m, -CH₂CH₂N = and 20-CH₂CH₃), 2.61(2H, t,
 J = 6.2Hz, -COCH₂CH₂O), 3.02~3.58(6H, m, 7-CH₂CH₃, -NHCH₂CH₂N = and OCH₂CH₃), 3.62~3.80(2H, m,
 -COCH₂CH₂O), 4.80~5.10(1H, br, 20-OH), 5.13(2H, dd, J = 18.7Hz, 5-H₂), 5.55(2H, dd, J = 11.4Hz, 17-H₂),
 7.38(1H, t, J = 5.5Hz, -NHCH₂CH₂N =), 7.56(1H, t, 10-H), 7.60(1H, s, 14-H), 7.74(1H, t, 11-H), 7.96(1H, d, 9-H),
 8.14(1H, d, 12-H).

Example 43

(Preparation of 7-ethyl-17-(N-tert-butoxycarbonyl-L-alanyloxy)campto thecin-21-(2-dimethylamino)-ethylamide)

5 To the salt-ice-cooled solution of tert-butoxycarbonyl-L-alanine (517 mg, 2.73mmol) in THF(15ml), triethylamine(0.38ml, 2.73mmol) and iso-butyl chloroformate(373mg, 2.73mmol) were added and the reaction mixture was stirred for 5 minutes. After adding the solution of 7-ethyl-17-hydroxycamptotheacin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in THF(15ml) and 4-N,N-dimethylaminopyridine(100mg, 0.82mmol), the reaction mixture was stirred for an hour under ice-cooling and then for 3 hours at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were dissolved in CHCl_3 and washed with a saturated aqueous solution of NaHCO_3 and with a saturated aqueous slution of NaCl . The organic phase was separated, dried with anhydrous MgSO_4 , and then evaporated to dryness under reduced pressure. The residual materials were purified through silica gel column chromatography with $\text{CHCl}_3\text{-MeOH}$ as an eluent and crystallized from $\text{CHCl}_3\text{-n-hexane}$ to give pale yellow crystals of the title compound(91mg, 7.9% in yield).

m.p. ~130 °C (dec.)

IR ν (KBr)cm⁻¹; 3340, 2970, 2930, 1735, 1705, 1650, 1595, 1510, 1450, 1160.

20 NMR(CDCl_3) δ ppm; 1.07(3H, t, J = 7.3Hz, 20- CH_3CH_3), 1.28~1.48(15H, m, 7- CH_2CH_3 , - $\text{CH}(\text{CH}_3)$ - and - $\text{C}(\text{CH}_3)_3$), 2.20~2.53(4H, m, - $\text{CH}_2\text{CH}_2\text{N} =$ and 20- CH_2CH_3), 2.25(6H, s, - $\text{N}(\text{CH}_3)_2$), 3.15(2H, q, 7- CH_2CH_3), 3.27~3.50(2H, m, - $\text{NHCH}_2\text{CH}_2\text{N} =$), 4.13~4.30(1H, m, $\text{COCH}(\text{CH}_3)\text{NHCO}$), 4.63~5.04(1H, br, 20-OH), 5.17~(2H, dd, J = 18.7Hz, 5-H₂), 5.28(1H, d, J = 6.6Hz, $\text{COCH}(\text{CH}_3)\text{NHCO}$), 5.62(2H, dd, J = 11.0Hz, 17-H₂), 7.46~(1H, br-t, - $\text{NHCH}_2\text{CH}_2\text{N} =$), 7.61(1H, t, 10-H), 7.68(1H, s, 14-H), 7.76(1H, t, 11-H), 8.04(1H, d, 9-H), 8.18(1H, d, 12-H).

25

Example 44

(Preparation of 7-ethyl-17-nicotinoyloxycamptotheacin-21-(2-dimethylamino)ethylamide and its dihydrochloride)

30 To the ice-cooled DMF solution(10ml) of 7-ethyl-17-hydroxycamptotheacin-21-(2-dimethylamino)-ethylamide(1.00g, 2.15mmol), the DMF solution (10ml) of nicotinoyl chloride hydrochloride(575mg, 3.23mmol) was added in the presence of 4-N,N-dimethylaminopyridine(100mg, 0.82mmol). The reaction mixture was stirred for an hour under ice-cooling and for 0.5 hours at room temperature. Then the reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were dissolved in CHCl_3 and washed with a saturated aqueous solution of NaHCO_3 and with a saturated aqueous solution of NaCl . The organic phase was separated, dried with anhydrous Na_2SO_4 , then evaporated to dryness under reduced pressure. The resulting materials were purified through silica gel column chromatography with $\text{CHCl}_3\text{-MeOH}$ as an eluent and crystallized from $\text{CHCl}_3\text{-n-hexane}$ to give pale yellow crystals of the title compound (157 mg, 12.8% in yield).

m.p. ~162 °C (dec.)

IR ν (KBr)cm⁻¹; 3360, 2970, 2930, 1715, 1645, 1590, 1510, 1275, 1110.

Dihydrochloride

45

To the suspension of free compound(120mg) in distilled water(20ml) 0.1N HCl(4.6ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the dihydrochloride as a yellow amorphous solid (126mg, 93.3% in yield).

IR ν (KBr)cm⁻¹; 3375, 2680, 1730, 1645, 1590, 1520, 1460, 1290, 1130.

50 NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J = 7.3Hz, 20- CH_3CH_3), 1.32(3H, t, J = 7.7Hz, 7- CH_2CH_3), 2.13~2.38(2H, m, 20- CH_2CH_3), 2.72 and 2.73(two 3H's, s, $\text{NH}^+(\text{CH}_3)_2$), 3.02~3.64(6H, m, 7- CH_2CH_3 and $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 5.32(2H, s, 5-H₂), 5.73(2H, dd, J = 11.0Hz, 17-H₂), 6.30~6.75(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.60~7.78 (2H, m, 10-H and Py), 7.86(1H, t, 11-H), 8.20(1H, d, 9-H), 8.24~8.37(2H, m, 12-H and Py), 8.49(1H, t, J = 5.5Hz, - $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$), 8.84(1H, dd, J = 1.8 and 5.1Hz, Py), 9.06(1H, d, J = 1.5Hz, Py), 10.22~10.42(1H, br, - $\text{NHCH}_2\text{CH}_2\text{NH}^+ =$).

Example 45

(Preparation of 7-ethyl-17-iso-nicotinoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its dihydrochloride)

5

Using iso-nicotinoyl chloride hydrochloride(575mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 44, whereby yellow crystals of the title compound(445mg, 36.3% yield) were obtained.

m.p. 168~171 °C (dec.)

10 IR ν (KBr)cm⁻¹; 3350, 2960, 2930, 1720, 1645, 1595, 1510, 1275, 1120.

Dihydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(7.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the dihydrochloride as a yellow amorphous solid in quantitative yield.

15 IR ν (KBr)cm⁻¹; 3360, 2675, 1725, 1645, 1590, 1510, 1280, 1120.

18 NMR(DMSO-d₆) δ ppm; 0.89(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.32(3H, t, J = 7.3Hz, 7-CH₂CH₃), 2.14~2.38(2H, m, 20-CH₂CH₃), 2.72 and 2.73(two 3H's, s, NH⁺(CH₃)₂), 3.02~3.63(6H, m, 7-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 5.33(2H, s, 5-H₂), 5.77(2H, dd, J = 11.0Hz, 17-H₂), 6.26~6.80(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.74(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91(2H, d, J = 5.1Hz, Py), 8.21(1H, d, 9-H), 8.30(2H, d, 12-H), 8.51(1H, t, J = 5.5Hz, -NHCH₂CH₂NH⁺ =), 8.87(2H, d, Py), 10.29~10.47(1H, br, -NHCH₂CH₂NH⁺ =).

Example 46

25

(Preparation of 7-ethyl-17-picolinoyloxycamptothecin-21-(2-dimethylamino)ethylamide)

Using picolinoyl chloride hydrochloride(575mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 44, whereby the yellow crystals of the title compound(23mg, 1.9% in yield) were obtained.

30 m.p. ~154 °C (dec.)

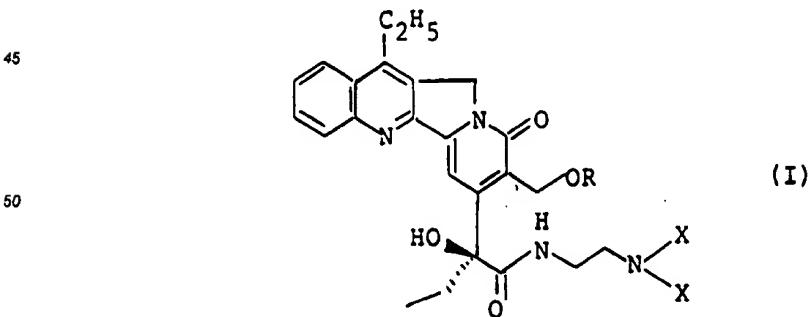
IR ν (KBr)cm⁻¹; 3370, 2960, 2930, 1715, 1650, 1595, 1510, 1455, 1305, 1285, 1245, 1130.

35 NMR(CDCl₃) δ ppm; 1.06(3H, t, J = 7.3Hz, 20-CH₂CH₃), 1.38(3H, t, J = 7.3Hz, 7-CH₂CH₃), 2.15~2.55(4H, m, 20-CH₂CH₃ and NHCH₂CH₂NH⁺ =), 2.23(3H, s, NH(CH₃)₂), 3.16(2H, q, 7-CH₂CH₃), 3.26~3.50(2H, m, NHCH₂CH₂NH⁺ =), 5.07~5.53(1H, br, 20-OH), 5.19(2H, s, 5-H₂), 5.87(2H, dd, J = 11.4Hz, 17-H₂), 7.50(1H, br, -NH-), 7.62(1H, t, 10-H), 7.65(1H, s, 14-H), 7.74~7.85(2H, m, 11-H and Py), 8.06(1H, d, 9-H), 8.13~8.23(2H, m, 12H and Py), 8.65~8.70(1H, m, Py).

Claims

40

1. Camptothecin derivatives of the general formula:



wherein

X is a C₁-C₆ alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or

branched unsubstituted C₁-C₁₈ alkyl group; a C₁-C₆ alkyl group substituted by a halogen atom or a C₁-C₆ alkylthio, amino, acylamino, hydroxyl, C₁-C₆ alkoxy, phenoxy or naphthoxy or C₁-C₆ alkoxy carbonyl group; a C₃-C₁₉ alkenyl, C₃-C₁₉ alkynyl or C₃-C₈ cycloalkyl group; a C₃-C₈ cycloalkyl group substituted by an acylamino-C₁-C₆ alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkyl, phenyl or C₁-C₆ alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thieryl group.

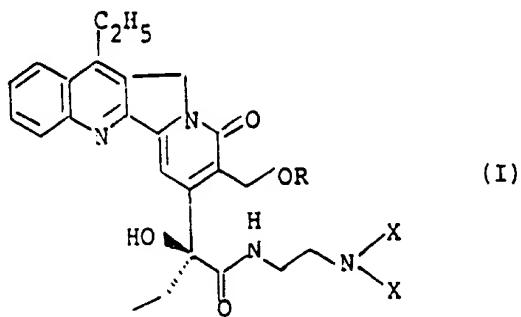
wherein the acyl moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids, and halogen- or hydroxy-substituted derivatives thereof, and their acid addition salts formed at the amino group and quaternary ammonium salts.

2. A process for the preparation of camptothecin derivatives of the general formula:

15

20

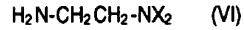
25



wherein

X is a C₁-C₆ alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C₁-C₁₈ alkyl group; a C₁-C₆ alkyl group substituted by a halogen atom or a C₁-C₆ alkylthio, amino, acylamino, hydroxyl, C₁-C₆ alkoxy, phenoxy or naphthoxy or C₁-C₆ alkoxy carbonyl group; a C₃-C₁₉ alkenyl, C₃-C₁₉ alkynyl or C₃-C₈ cycloalkyl group; a C₃-C₈ cycloalkyl group substituted by an acylamino C₁-C₆ alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkyl, phenyl or C₁-C₆ alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thieryl group.

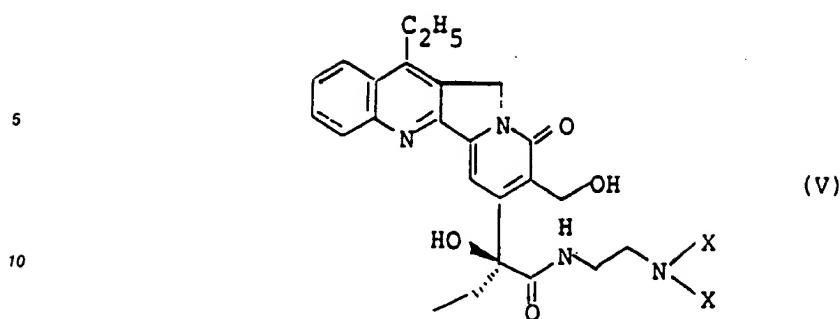
wherein the acyl moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids, and halogen- or hydroxy-substituted derivatives thereof, and their physiologically acceptable acid-addition salts at the amino group, which comprises treating 7-ethylcamptothecin with an ethylenediamine derivative of the general formula:



wherein X has the same meaning as given above, to form a 7-ethyl-17-hydroxymethylcamptothecin-21-(2-dialkylamino)ethylamide of the general formula:

50

55



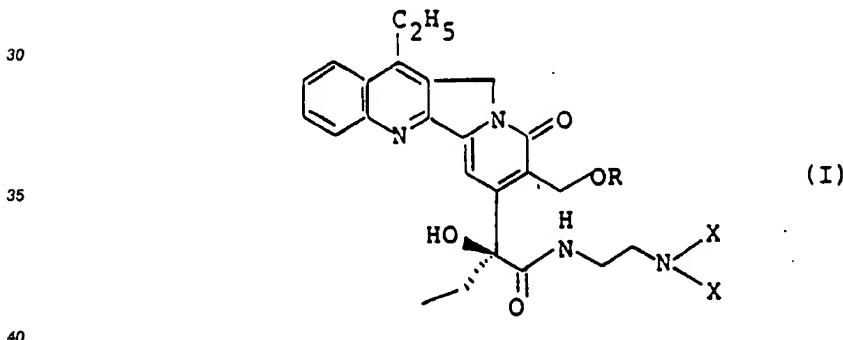
15 wherein X has the same meaning as given above, and if necessary, acylating the resultant compound of the general formula (V) with a compound of the general formula:

Z-COY (VII)

20 wherein Y has the same meaning as given above and Z is a hydroxyl group, a halogen atom or the grouping -O-COY, and if desired, converting the resultant compound of the general formula (I) into its physiologically acceptable acid addition salt or quaternary ammonium salt or vice versa.

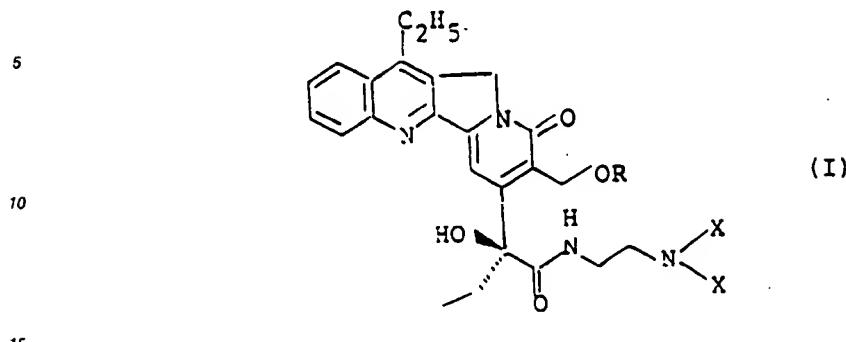
Patentansprüche

25 1. Camptothecinderivate der allgemeinen Formel



in der
 X einen C₁-C₆-Alkylrest bedeutet, und R ein Wasserstoffatom oder den Rest -COY darstellt, in dem Y einen unverzweigten oder verzweigten unsubstituierten C₁-C₁₈-Alkylrest; einen C₁-C₆-Alkylrest, der mit einem Halogenatom oder einem C₁-C₆-Alkylthiorest, einer Aminogruppe, einem Acylaminorest, einer Hydroxylgruppe, einem C₁-C₆-Alkoxyrest, einer Phenoxy- oder Naphthoxygruppe oder einem C₁-C₆-Alkoxy carbonylrest substituiert ist; einen C₃-C₁₉-Alkenyl-, C₃-C₁₉-Alkinyl- oder C₃-C₈-Cycloalkylrest; einen C₃-C₈-Cycloalkylrest, der mit einem Acylamino-C₁-C₆-alkylrest substituiert ist; einen N-Acylpyrrolidylrest; eine Phenylgruppe; eine mit einem Halogenatom oder einer Trifluormethyl-, Nitro- oder Aminogruppe, einem C₁-C₆-Alkoxy carbonyl- oder C₁-C₆-Alkylrest oder einer Phenylgruppe oder einem C₁-C₆-Alkoxyrest substituierte Phenylgruppe; eine Cinnamylgruppe; eine Benzylgruppe; eine Naphthylgruppe; eine Pyridylgruppe; eine Furylgruppe; oder eine Thienylgruppe; bedeutet, wobei der Acylanteil der Acylamino- und N-Acylpyrrolidylreste den Rest einer Säure bedeutet, die vorzugsweise ausgewählt ist aus aliphatischen und aromatischen Carbonsäuren, einschließlich Aminosäuren, aliphatischen und aromatischen Sulfonsäuren und deren halogen- oder hydroxysubstituierten Derivaten, und deren an der Aminogruppe gebildete Säureadditionssalze und quartär Ammoniumsalz.

2. Verfahren zur Herstellung von Camptotheccinderivaten der allgemeinen Formel

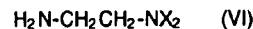


in der

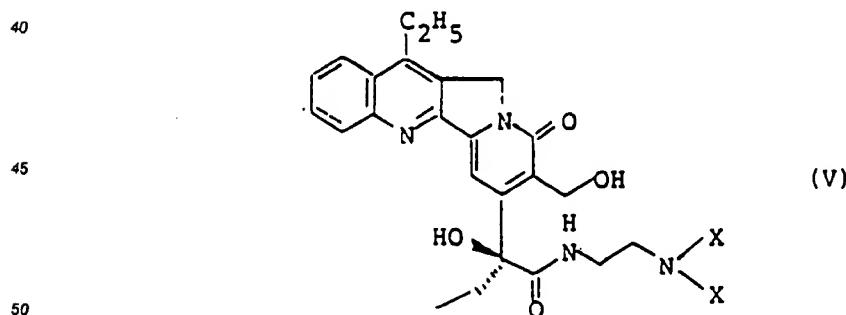
20 X einen C₁-C₆-Alkylrest bedeutet, und R ein Wasserstoffatom oder den Rest -COY darstellt, in dem Y einen unverzweigten oder verzweigten unsubstituierten C₁-C₁₈-Alkylrest; einen C₁-C₆-Alkylrest, der mit einem Halogenatom oder einem C₁-C₆-Alkylthiorest, einer Aminogruppe, einem Acylaminorest, einer Hydroxylgruppe, einem C₁-C₆-Alkoxyrest, einer Phenoxy- oder Naphthoxygruppe oder einem C₁-C₆-Alkoxycarbonylrest substituiert ist; einen C₃-C₁₉-Alkenyl-, C₃-C₁₉-Alkinyl- oder C₃-C₈-Cycloalkylrest; einen C₃-C₈-Cycloalkylrest, der mit einem Acylamino-C₁-C₆-alkylrest substituiert ist; einen N-Acylpyrrolidylrest; eine Phenylgruppe; eine mit einem Halogenatom oder einer Trifluormethyl-, Nitro- oder Aminogruppe, einem C₁-C₆-Alkoxy carbonyl- oder C₁-C₆-Alkylrest oder einer Phenylgruppe oder einem C₁-C₆-Alkoxyrest substituierte Phenylgruppe; eine Cinnamylgruppe; eine Benzylgruppe; eine Naphthylgruppe; eine Pyridylgruppe; eine Furylgruppe; oder eine Thienylgruppe; bedeutet, wobei der Acylanteil der Acylamino- und N-Acylpyrrolidylreste den Rest einer Säure bedeutet, die vorzugsweise ausgewählt ist aus aliphatischen und aromatischen Carbonsäuren, einschließlich Aminosäuren, aliphatischen und aromatischen Sulfonsäuren und den halogen- oder hydroxysubstituierten Derivaten davon, und ihren physiologisch verträglichen, mit der Aminogruppe gebildeten Säureadditionssalzen, umfassend die Umsetzung von 7-Ethylcamptotheccin mit einem Ethyldiaminderivat der allgemeinen Formel:

25

30



in der X die vorstehend angegebene Bedeutung hat, zu einem 7-Ethyl-17-hydroxymethylcamptotheccin-21-(2-dialkylamino)ethylamidder allgemeinen Formel:



in der X die vorstehend angegebene Bedeutung hat, und falls erforderlich, das Acylieren der erhaltenen Verbindung der allgemeinen Formel (V) mit einer Verbindung der allgemeinen Formel

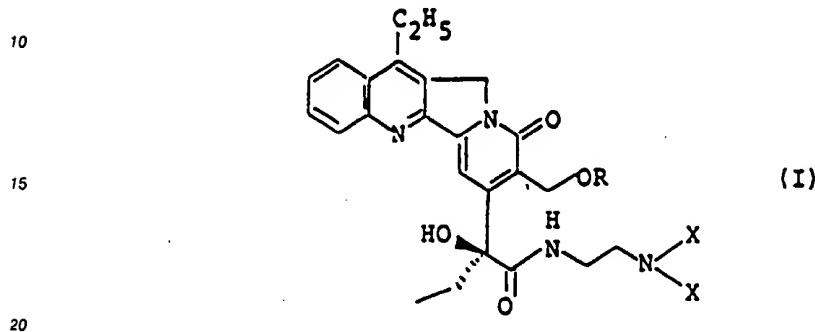


in der Y die vorstehend angegebene Bedeutung hat und Z eine Hydroxylgruppe, ein Halogenatom oder

den Rest -O-COY bedeutet, und falls gewünscht, das Umwandeln der erhaltenen Verbindung der allgemeinen Formel (I) in ihr physiologisch verträgliches Säureadditionssalz oder quartäres Ammoniumsalz oder umgekehrt.

5 Revendications

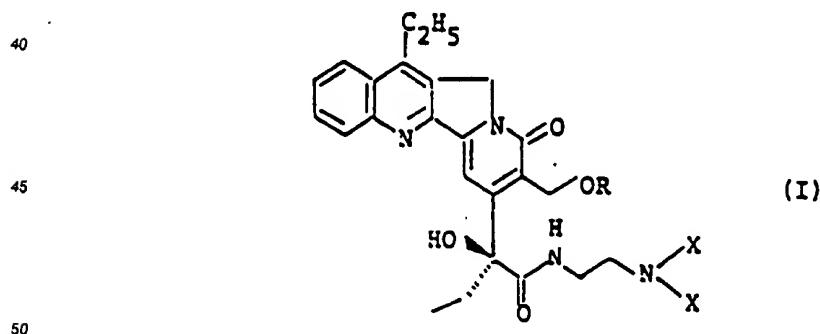
1. Dérivés de camptothécine de formule générale :



dans laquelle

X est un groupe alkyle en C₁-C₆ et R est un atome d'hydrogène ou le groupement -COY, où Y est un groupe alkyle en C₁-C₁₈ non substitué, linéaire ou ramifié ; un groupe alkyle en C₁-C₆ substitué par un atome d'halogène ou un groupe alkylthio en C₁-C₆, amino, acylamino, hydroxyle, alcoxy en C₁-C₆, phényloxy, naphtyloxy ou (alcoxy en C₁-C₆)carbonyle ; un groupe alcényle en C₃-C₁₉, alcynyle en C₃-C₁₉ ou cycloalkyle en C₃-C₈ ; un groupe cycloalkyle en C₃-C₈ substitué par un groupe acylamino-alkyle en C₁-C₆ ; un groupe N-acylpypyrrolidyle ; un groupe phényle ; un groupe phényle substitué par un atome d'halogène ou un groupe trifluorométhyle, nitro, amino, (alcoxy en C₁-C₆)carbonyle, alkyle en C₁-C₆, phényle ou alcoxy en C₁-C₆ ; un groupe cinnamyle ; un groupe benzyle ; un groupe naphtyle ; un groupe pyridyle ; un groupe furyle ; ou un groupe thiényle, où le fragment acyle dans les groupes acylamino et N-acylpypyrrolidyle est un reste d'un acide choisi de préférence parmi les acides carboxyliques aliphatiques et aromatiques, y compris les amino-acides, les acides sulfoniques aliphatiques et aromatiques et leurs dérivés halogéno- ou hydroxy-substitués, et leurs sels d'addition d'acides formés sur le groupe amino et leurs sels d'ammonium quaternaire.

2. Un procédé pour la préparation de dérivés de camptothécine de formule générale :



dans laquelle

X est un groupe alkyle en C₁-C₆ et R est un atome d'hydrogène ou le groupement -COY, où Y est un groupe alkyle en C₁-C₁₈ non substitué, linéaire ou ramifié ; un groupe alkyle en C₁-C₆ substitué par un atome d'halogène ou un groupe alkylthio en C₁-C₆, amino, acylamino, hydroxyle, alcoxy en C₁-C₆, phényloxy, naphtyloxy ou (alcoxy en C₁-C₆)carbonyle ; un groupe alcényle en C₃-C₁₉, alcynyl en C₃-C₁₉ ou cycloalkyle en C₃-C₈ ; un groupe cycloalkyle en C₃-C₈ substitué par un groupe acylamino-alkyle en C₁-C₆ ; un groupe N-acylpypyrrolidyle ; un groupe phényle ; un groupe phényle substitué par

un atome d'halogène ou un groupe trifluorométhyle, nitro, amino, (alcoxy en C₁-C₆)carbonyl, alkyle en C₁-C₆, phényle ou alcoxy en C₁-C₆ ; un group cinnamyle ; un groupe benzyl ; un groupe naphtyle ; un groupe pyridyle ; un groupe furyle ; ou un groupe thiényle,

5 où le fragment acyle dans les groupes acylamino et N-acylpiperidyle est un reste d'un acide choisi de préférence parmi les acides carboxyliques aliphatiques et aromatiques, y compris les amino-acides, les acides sulfoniques aliphatiques et aromatiques et leurs dérivés halogéno- ou hydroxy-substitués, et leurs sels d'addition d'acides physiologiquement acceptables formés sur le groupe amino, qui comprend le traitement de la 7-éthylcamptothécine avec un dérivé d'éthylénediamine de formule générale :

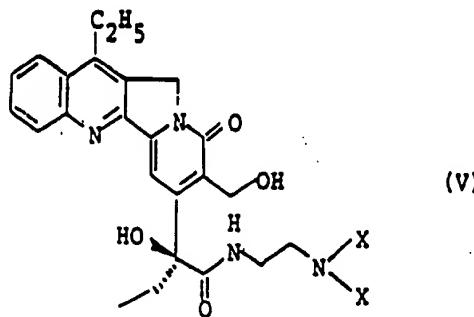
10 H₂N-CH₂CH₂-NX₂ (VI)

dans laquelle X a la même signification que ci-dessus, pour former un 7-éthyl-17-hydroxyméthylcamptothécine-21-(2-dialkylamino)éthylamidé de formule générale :

15

20

25



30 dans laquelle X a la même signification que ci-dessus, et, le cas échéant, l'acylation du composé obtenu de formule générale (V) avec un composé de formule générale :

Z-COY (VII)

35 dans laquelle Y a la même signification que ci-dessus et Z est un groupe hydroxyle, un atome d'halogène ou le groupement -O-COY, et, si on le désire, la conversion du composé obtenu de formule générale (I) en son sel d'addition d'acide physiologiquement acceptable ou son sel d'ammonium quaternaire ou vice et versa.

40

45

50

55